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Editorial

Coronary atherosclerosis Status of MER-29 (triparanol)

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Various epigrams attempt to characterize man. He is a social animal, but he shares this propensity with the rat[1] and other species. He is a rational biped, but he often acts irrationally. Homer Smith gets closer to a definition by describing him in terms of highly developed consciousness.[2] It is this and its corollary, the ability to reflect, that makes him the supremely expedient animal. Confronted with a problem, he solves it, gets around it, or rationalizes it, often thereby creating new problems, so that the process repeats indefinitely. Thus, faced with heavy loads and a weak back, his strong mind invented the wheel. The wheel led him to make roads; roads led to the invention of the horse-collar and of wagon springs, and ultimately, to the automobile, with all its attendant hazards.

Some of these expedients and solutions have been unexpectedly disadvantageous. Thus, thanks to human ingenuity, a powerful and vocal part of mankind enjoys "the more abundant Life" and is both sedentary and overfed. The snake in this greasy garden is the high prevalence of coronary atherosclerosis, with its sequelae of arteriosclerotic heart disease and myocardial infarction in young men and middle-aged men and women. As a nation we feel this more than most. However, the problem arises in every group capable of relatively easy living. Perhaps our economists could get better insight into the relative status of a country such as Russia from statistics on coronary heart disease than from estimates of production of commodities.

We do not seem to recognize the fact that we have rational, if incomplete, solutions to this great social problem, nor do we act on this knowledge. As Olson[3] has pointed out, we know as much about the real causes of coronary atherosclerosis as we do about tuberculosis; Koch's postulates have been fulfilled, and, if we still cannot explain many cases of coronary heart disease, it is also true that we cannot explain every case of tuberculosis. Physical exercise tends to prevent or delay atherogenesis[4]; the prevalence of coronary atherosclerosis increases with the use of diets rich in calories, especially fat calories and particularly most hard fats.[5] Indeed, diet and exercise seem to be largely two sides of the same coin. Skeletal and heart muscle[6] use more fatty acid for energy than they do carbohydrate, and, if diet

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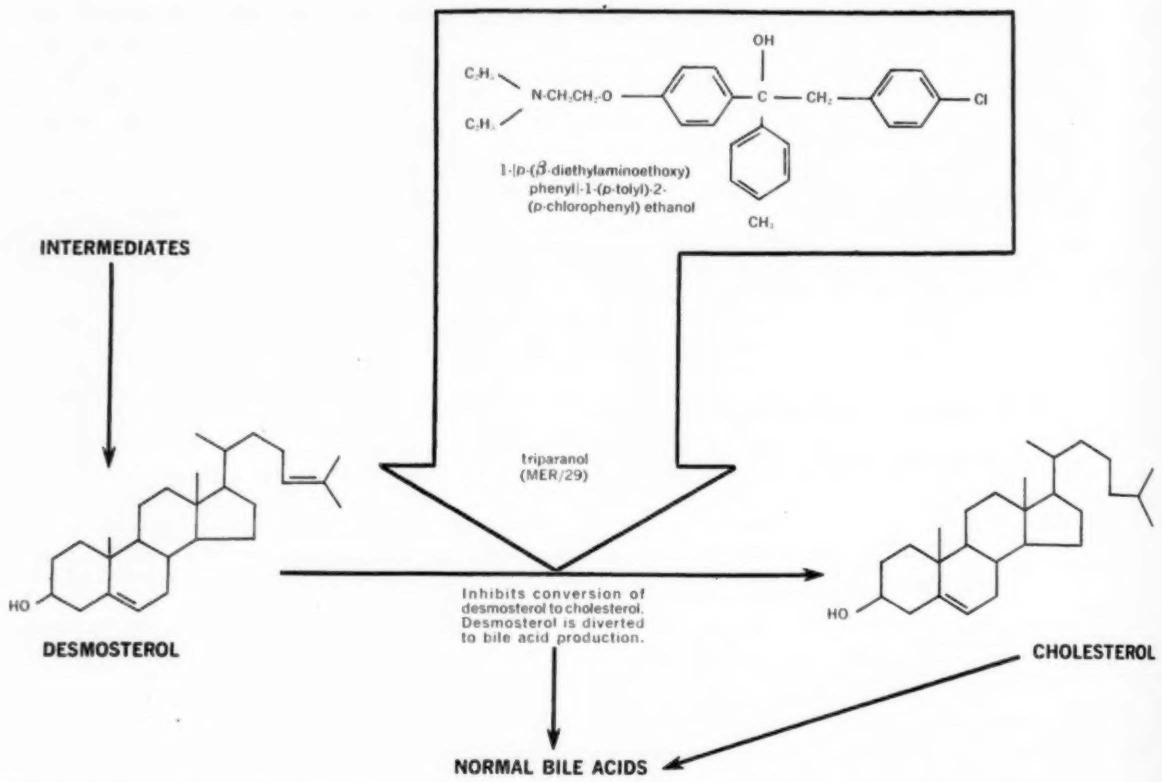

Fig. *1*. Schema illustrating structure and action of MER-29.

provides more fat precursors or "stress" mobilizes more fatty acid than the muscles use, the excess fat circulates preferentially in the beta-lipoproteins. Then, assuming the filtration concept of atherogenesis,[7] some of these fragile and bulky molecules decompose in the intima as plasma filters through. The soluble protein and miscible phosphatide fractions move on; fat and cholesterol accumulate, the tissue reacts, and atherogenesis begins.

Of course, this is an oversimplification. Heredity, anatomy, arterial pressure, emotional and endocrine status, and nonlipid dietary factors all have to be considered. Correspondingly, the report on diet and atherogenesis recently released by the American Heart Association[8] includes many reservations. Nevertheless, much more directly than its predecessor[9] it does recommend "reduction or control of fat consumption under medical supervision, with reasonable substitution of poly-unsaturated for saturated fats" as a possible means of preventing atherosclerosis. The recommendation applies specifically to coronary atherosclerosis. There is little or no evidence to suggest that diet or exercise bear on the genesis of aortic atherosclerosis. These may be distinct entities linked by misleadingly similar lesions.

If we were not so given to expedients, the way would be clear. In order to prevent or delay most coronary atherosclerosis we should begin systematic programs of diet and exercise in youth and continue these through life. Unfortunately, asceticism is more admired than practised. The search for medicinal expedients began years ago. The first was iodide. Given to rabbits in doses that cause iodism in man, it delayed atherogenesis by impairing their appetite for fat and cholesterol diets. It may have had some specific antiatherogenic effects, related possibly to formation of thyroid analogues, with small, fleeting oxidative and large lipopenic effects. Soya lecithin was advocated: it is moderately distasteful, fairly bulky, suppresses appetite, and provides unsaturated fat. Recently, unsaturated fat has been used as such; it also inhibits appetite and, isocalorically substituted for saturated fat, lowers the level of serum lipid and cholesterol. More practical, but more appetizing, is substitution of unsaturated for saturated fat in palatable,

normal diets.[10] Lipocaic, among other agents, may have some effect on transport of fat, and injected heparin certainly has. Another approach is to impair intestinal absorption of cholesterol directly, as with sitosterol, or indirectly by sequestering cholic acid,[11] again with the requirement of bulky before-meal medication. Lastly, large doses of nicotinic acid often depress serum cholesterol. The mechanism of this action is not clear; liver damage has been described, and effective doses usually provoke distressing side effects of flushing and pruritus. In brief, none of these expedients is really convenient.

The ideal would be an agent that, in small doses, would specifically decrease availability of cholesterol for beta-lipoprotein synthesis. Among agents tested, phenylpropionic acid has this effect on liver slices; the data are not convincing that it has hypocholesterolemic effect in vivo. A much more regularly effective agent was thoroughly discussed at a conference held in December, 1959.[12] This compound, MER-29 (triparanol), inhibits saturation of the C_{24}-C_{25} double bond (Fig. 1). The inhibition results in a new body-sterol equilibrium in which the immediate precursor of cholesterol, desmosterol, substitutes for some of the cholesterol of blood and non-neural tissues. If substitution were all that occurred, and if desmosterol were as atherogenic as cholesterol—so far, no one knows whether it is or is not—the compound might be only of academic interest. What makes it important is that accumulation of desmosterol seems to slow down synthesis of *its* precursors, so that the total body-sterol pool decreases. The dynamic equilibrium of cholesterol then tends to deplete cholesterol from storage sites, including experimental atheroma.

The remarkable thing is that this depletion seems to occur clinically in patients with arteriosclerotic heart disease. This has not been directly demonstrated, except that regression of xanthelasma in a hypercholesterolemic patient given MER-29 suggests that it may occur (Fig. 2). However, studies of more than 1 year's duration at the time of the Conference, and more than 2 years now, indicate that a substantial proportion of patients with angina pectoris improve, with reversion toward normal of electrocardiographic changes in some and decreases in serum cholesterol and lipid in most, especially in those initially hyperlipemic. Of course, angina is a difficult thing to evaluate. It can improve "spontaneously"; it is highly conditioned by emotions and suggestions; nitroglycerin requirement is a more or less dubious datum; even exercise tolerance tests may be misleading measures of changing status. Hence, the impact of the evidence lies more in its mass and direction than in any single criterion that proves what indirect evidence suggests is regression of atheromata.

Few undesirable side effects were described at the Conference. For the most part, these were rashes and gastric irrita-

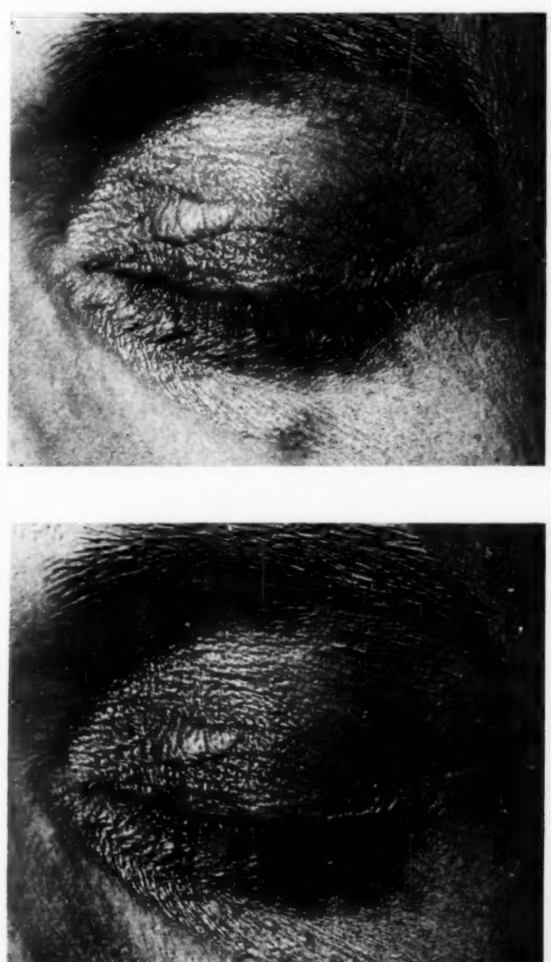

Fig. 2. Equal magnifications of xanthelasma of the left eyelid before (above) and after (below) 6 months of treatment with MER-29. The serum cholesterol before was about 300, and during treatment about 160 mg. per 100 ml.

tion in about the proportion that would occur from taking aspirin. The manufacturer's current estimates indicate that these occur in less than 2 per cent of patients. Specific toxic effects were not observed even when the dosage was increased to as much as 10 times the usual 250 mg. daily; large doses do not further impair hepatic function in patients with liver disease, although they may have little effect on the low levels of serum cholesterol in these patients.[13] In this respect, MER-29 differs substantially from Benzmalacene, an agent that interferes with the acetate conjugations that are the first steps in cholesterol synthesis. Since such conjugations underlie many other important reactions, it is not surprising that the drug was unpleasantly hepatotoxic.[14] Thus, the low toxicity of MER-29 is a result of its acting only on the last step in cholesterol synthesis. Recently, very large doses of MER-29 have been reported to impair adrenal cortical response to ACTH,[15] possibly by limiting the available supply of adrenal cholesterol. However, among patients taking the drug in doses of 250 or 500 mg. daily for months or years, signs of deficient adrenal function have not been recognized.

MER-29 was marketed about a year ago and with a vastly better background of basic and clinical study than most agents, including, for example, sulfanilamide. Physicians' opinions as to its effectiveness vary. Some, whose first patients responded well, are enthusiastic; some have been disappointed by transient responses, and others discouraged by examples of resistance. The lack of unanimity is understandable because few physicians can provide truly adequate pretreatment and post-treatment data from sufficient numbers of patients to formulate definite opinions based on personal experience. Some may start the drug shortly after a myocardial infarct has already altered serum cholesterol,[16] and some give it with other possibly hypocholesterolemic agents, or they may restrict or, more often, relax dietary control at the time it is prescribed.

The proportion of patients who respond by a decrease in serum cholesterol is usually described as 4 out of 5. A preliminary review of our experience with Dr. Henry Zimmerman suggests that it is closer to 3 out of 5. However, this experience includes 20 hospitalized patients whose courses of observation averaged only 2 weeks, some of whom had recent myocardial infarcts, and 50 office patients whose course of observation by Dr. Zimmerman averaged 6 months. Of these 50, 27 showed definite (more than 10 per cent decrease) and 5 doubtful responses; 2 of the nonresponders did respond when dosage was increased to 500 mg. daily, 3 had low levels of serum cholesterol to start with, and 7 were on heparin at the time treatment was started. Most of the patients had asymptomatic arteriosclerotic heart disease to start with and felt neither better nor worse as a result of treatment. Some described a feeling of well-being which may have reflected their conviction that they now saw a way out of a seemingly hopeless situation or their relief at relaxation of strict dietary control. A few seemed to be actually improved. Thus, a woman with essential hypercholesterolemia, whose serum level fell from 750 to about 400 mg. per 100 ml. on 250 mg. of MER-29 daily, described disappearance of angina; interestingly, this recurred at a serum cholesterol of 250 mg. per 100 ml. when 4 mg. of dextro-thyroxine was added to her regimen. A personal communication from Dr. Jorge Martins de Oliveira, of Rio de Janeiro, describes relief of angina in 25 of 30 patients under treatment; in 6 this was associated with electrocardiographic improvement; group means of serum levels of cholesterol and beta-lipoprotein decreased, whereas alpha-lipoprotein increased. Neither Dr. Zimmerman's nor Dr. Martins' series indicated the appearance of major side effects attributable to the drug.

Webster's New World Dictionary lists two meanings of the term *expedient,* i.e., "something useful for effecting a desired result" or "based on or offering what is of use or advantage rather than what is right and just." In brief, an expedient must be effective and it may be either "good" or "bad." Possibly the procedure best directed toward delaying onset of coronary arteriosclerosis would be a wholesale, fairly drastic change in exercise and dietary patterns from youth on. But this might be

injurious to some and ineffective in most if it were vigorously and indiscriminately applied to people of middle age, some of whom have already significant arteriosclerotic heart disease. Certainly these people do require reasonable, individualized, acceptable hygienic guidance. Many need more than this, especially those who are hypercholesterolemic, i.e., those who have a serum cholesterol over about 2[illegible]0 mg. per 100 ml. For most of these, MER-29 seems to be fairly effective and, to use the moral judgment, "right and just," and therefore the best simple expedient available. What the drug can do by itself toward preventing coronary atherosclerosis we will not know until systematic longitudinal surveys have compared prevalences of arteriosclerotic heart disease in large numbers of control and treated subjects over several years.

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Clinical communications

Contributions to the functional morphology of the P wave

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Technical progress has greatly facilitated a more detailed analysis of the P wave by means of scalar electrocardiography (high-fidelity electrocardiography[1]) and by electrical dissection of the vectorcardiogram (differential vectorcardiography[2]). Nothwithstanding, the conventional electrocardiogram still supplies a major amount of information on this wave. Much effort has been expended on increasing our knowledge of atrial activity. The original, but laborious, method of Abildskov[3] for the study of atrial activation, and the simple but practical criteria of Macruz and associates[4] for the recognition of atrial enlargement serve the same purpose.

In the present study, using the conventional electrocardiogram, some morphologic particularities of the P wave have been investigated by methods not previously employed.

The normal peaked P wave and especially its pathologic counterpart present a triangular shape, the angles of which can be easily and accurately measured. With certain limitations, the same method can also be applied to the study of the rounded P waves. Therefore, the angular structure of the normal P wave was investigated, and its correlation with cardiac rate and with age was established. The concept of rising time and rising velocity in normal subjects has been established.

The electrocardiographic pattern of pulmonale P wave was investigated by means of these new criteria in patients with chronic cor pulmonale. Acute pulmonale P was produced experimentally by breathing against manometric pressure and was analyzed in detail. Finally, the ratio of Macruz was systematically investigated in normal subjects and in subjects with chronic and experimentally produced acute right atrial overload, and its diagnostic value was critically assessed.

Methods and material

The conventional electrocardiogram recorded by a Sanborn Instomatic electrocardiograph with the subject in the recumbent position was used in the present study. According to the shape of the P wave, records were divided into two groups, those with peaked and those with rounded apex. For exact quantitation a magnifying lens was constantly used. A peaked P wave was considered to be present when the sharp pointed apex lasted not more than 0.01 second. Any other P waves with a longer-lasting apex with rectilinear or curvilinear configuration was considered to be rounded. All measurements were made in Lead II only. The height of the P wave was measured in millimeters, from the upper level of the base line to the peak of P. Duration of the P wave was determined from the onset of the P wave to the onset of the P-R segment. The P-R interval was measured from the onset of the P wave to the onset of the QRS complex and expressed in hundredths of a second. Duration of the P-R segment was calculated by substracting the length of the P wave from the length of the P-R interval. The surface

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area of the P wave was calculated by multiplying height with duration and then dividing this sum by 2. The result is expressed in microvolt-seconds (mvs). The rising time was determined (Fig. 1) by measuring the length of the projection of the ascending limb of the P wave on the base line. For this purpose a vertical line was dropped from the apex, and the distance from the onset of the P wave to the intersection of the vertical with the base line was measured and expressed in hundredths of a second and as a percentage of the duration of the P wave. The rising velocity of the P wave was calculated by dividing the height of the P wave by the rising time and was expressed in millimeters per 0.01 second.

All these definitions refer to the peaked P waves, the exclusive subject of the present study.

The index of Macruz was calculated by dividing the duration of the P wave by the length of the P-R segment as described previously.

Of the angles which form the atrial triangle, only angles α and β were measured directly, whereas angle γ was calculated according to the formula $\gamma = 180° - (\alpha + \beta)$. The ascending and descending limbs of the peaked P wave in normal cases and especially in cases with abnormally increased height can easily be extended by using a ruler. The angle formed by the lines of prolongation of the limbs of the P wave with the horizontal lines of the electrocardiographic record can be accurately measured by a goniometer.

For the study of experimentally produced acute pulmonary P the following method was used (Gross[5]). After the conventional electrocardiogram had been recorded with the subject in the decubitus position, an ordinary blood pressure apparatus was placed on a table at the side of the recumbent subject and at the height of his line of vision, so that he could observe the movement of the column of mercury during the performance of the test. Cuff connection of the apparatus was removed and replaced by a rubber tube, 50 cm. in length, provided with a convenient glass mouthpiece. The subject was instructed to blow, after a deep inspiration, into the tube connected with the manometer so as to elevate

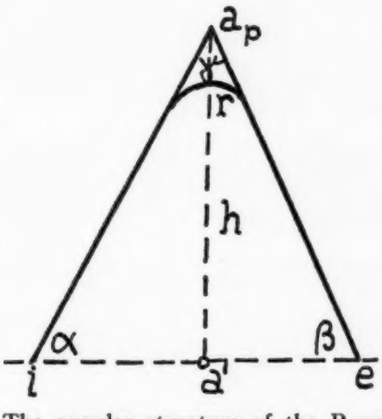

Fig. *1*. The angular structure of the P wave and geometrical representation of the rising time and rising velocity. a_p: Apex of the peaked P wave. a': Projection of the apex on the base line. i-a': Rising time. *h/rising time*: Rising velocity. a'-e: Fall time. r: Summit of the rounded P wave.

the column of mercury above 60 mm. and to sustain it for 15 seconds.

The correlation between the P wave and different cardiac rates was studied in groups, each containing 30 records from 51 to 110 beats per minute. Average values were calculated in each group. The correlation between the P wave and age was studied in three groups. The young age group comprised subjects under 20 years of age; the middle-aged group, subjects between 21 and 50 years of age; and the old age group, subjects over 51 years of age.

Results

Normal peaked P wave. Table I reproduces all the corresponding measured data.

Correlation between normal peaked P wave and cardiac rates (*Table II*). According to the observed data, cardiac rates cause change in the morphology of the P wave, in a certain sense, but there is a lack of strict quantitative parallelism.

Correlation between normal peaked P wave and age (*Table III*). The influence of age on the morphology of the P wave is very definite. The height of the P wave decreases but its duration and surface area increase with increasing age. The rising time increases and the rising velocity decreases very clearly with advancing years. The duration of the P-R interval is prolonged. Angle α decreases progressively, whereas the apical angle γ enlarges with increasing age. The index of Macruz also increases.

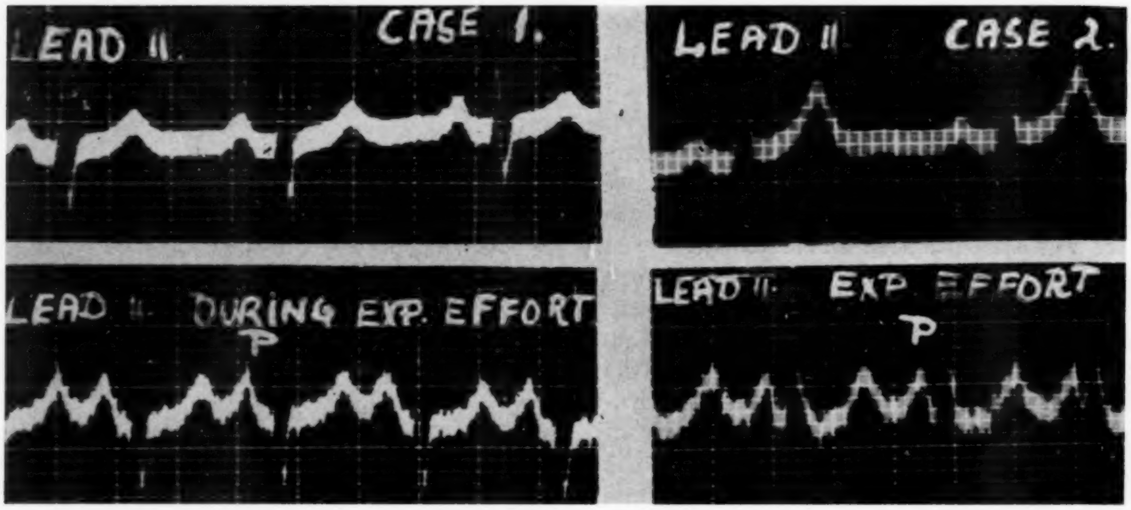

Fig. 2. Characteristic changes observed in two cases.

Cardiac patients presenting pulmonary P pattern (Table I). The pulmonary P wave in Lead II is 86 per cent higher, of equal duration, discloses a surface area 77 per cent larger than the normal P wave, presents a 3 per cent shorter rising time, and a rising velocity 82 per cent greater than the normal P wave. The P-R interval remains unaltered. The ratio of Macruz increases by 12 per cent. Both angles of the base of the atrial triangle increase, angle α by 38 per cent and angle β by 31 per cent. Consequently, angle γ decreases by 38.5 per cent.

Healthy subjects presenting experimentally produced acute pulmonary P wave. Fig. 2 shows tracings that very distinctly exhibit all the characteristic changes observed in this test.

CASE 1. Healthy male subject, 43 years old. The resting electrocardiogram presented normal sinus rhythm with 83 beats per minute. The P wave was 1.4 mm. in height, 0.11 second in duration, and its surface area measured 7.7 mvs. The rising time was 0.06 second; that represented 55 per cent of the duration of the P wave. The rising velocity measured 0.35 mm. per 0.01 second. Duration of the P-R interval was 0.17 second, and the index of Macruz was 1.83. Angle α measured 48°, angle β 65°, and angle γ 67°. The electrocardiogram registered during expiratory effort revealed a cardiac rate of 128 beats per minute, i.e., an acceleration of 41 beats per minute (+49 per cent). The acutely pointed P wave presented a height as great as 3.0 mm. (+ 114 per cent) and a duration of 0.10 second (−9 per cent). The surface area measured 15.0 mvs (+94 per cent). The rising time was 0.04 second (−43 per cent), representing 40 per cent of the duration of the P wave. The rising velocity increased to 0.43 mm. per 0.01 second (+23 per cent). Duration of the P-R interval shortened to 0.14 second (−18 per cent). The index of Macruz increased to 2.5 (+37 per cent). Angle α measured 60° (+25 per cent), angle β 72° (+10 per cent), and angle γ 48° (−29 per cent).

CASE 2. Young man, 30 years old. The resting electrocardiogram showed a regular sinus rhythm of 71 beats per minute. The height of the P wave measured 1.0 mm., and the duration was 0.10 second. Consequently, the surface area was 5.0 mvs. The rising time measured 0.045 second, 45 per cent of the duration of the P wave. The rising velocity was 0.25 mm. per 0.01 second. The P-R interval measured 0.16 second in length. The index of Macruz had a value of 1.66. Angle α was 55°, angle β 64°, and angle γ 61°. During expiratory effort the following alterations were observed. Cardiac rates increased to 107 beats per minute (a difference of 36 beats, +50 per cent). The height of the P wave increased to 3.2 mm. (+220 per cent) and lasted 0.08 second (−20 per cent). Therefore, the corresponding surface area measured 12.8 mvs (+156 per cent). The rising time increased to 0.06 second (+33 per cent), and

the rising velocity to 0.53 mm. per 0.01 second (+112 per cent). The P-R interval was 0.12 second in length (−25 per cent). The Macruz index was 2.0 (+20 per cent). The angle α was then 60° (+9 per cent), angle β 83° (+29 per cent), and angle γ 37° (−40 per cent).

Table IV contains all pertinent data observed in this group of 15 subjects. As a conclusion, we may state that expiratory effort caused acceleration of the heart rate by an average of 35 beats per minute. The height of the P wave increased by 48 per cent, its duration shortened by 17 per cent, and its surface area increased by 91 per cent. The rising time was prolonged by 22.5 per cent, and rising velocity increased by 73 per cent. The P-R interval was shortened by 17.5 per cent. The index of Macruz increased by 17 per cent. The basal angles of the atrial triangle α and β increased, 27 and 28 per cent, respectively, and the apical angle γ decreased by 38 per cent.

Discussion

The morphogenesis of the P wave is settled almost satisfactorily. Opinion is unanimous that the ascending limb of the P wave corresponds to the activation of the right atrium. Septal activation correlates with the inscription of the ascending segment of the P wave. Left auricular activation is related partly to the ascending portion and partly to the middle and lower third of the descending portion of the P wave. This correlation refers to the conventional Lead II, where all morphologic particularities of the P wave are most clearly present. Correlation of the rounded P wave to atrial activation is more speculative; in the present study the investigation is limited exclusively to the peaked P waves as inscribed in Lead II.

The magnitudes of the normal P wave observed in this study are in perfect accordance with general experience. The height of the P wave—1.24 mm. ± 0.42 (0.5 to 2.5 mm.)—is of the same order of magnitude as that indicated by Ashman and Hull,[6] i.e., 1.25 mm. (0.3 to 2.5 mm.), by Sano and associates,[7] i.e., 1.3-1.4 mm. (0.5 to 2.5 mm.), and by Stewart and Manning,[8] i.e., 1.4 mm. ± 0.53. The duration of the P wave was 0.097 second ± 0.014 (0.06 to 0.12 second), whereas the corresponding values indicated by other authorities were: 0.09 second ± 0.015 (0.07 to 0.12 second) by Sano and associates,[7] and 0.09 second (0.06 to 0.11 second) by Macruz and associates.[4]

The height of the P wave indicates the

Table I. The linear and angular structure of the peaked P wave in normal condition and in chronic cor pulmonale

	Age (yr.)	*Rate (min.)*	*Height (mm.)*	*Duration (sec.)*	*Surface area (mvs)*	*Rising time*		*Fall time (sec.)*	*Rising velocity (mm./0.01 sec.)*	*P-R (sec.)*	*Angle°*		
						sec.	*%*				α	β	γ
						Normal							
Mean	43.5	80	1.24	0.097	5.97	0.0512	53.3	0.0448	0.260	0.16	44.0	51.5	84.5
S.D.			0.42	0.014	2.18	0.0137	10.3	0.0115	0.111	0.022	9.6	10.3	19.7
Range	8	51	0.5	0.06	2.4	0.02	25.0	0.02	0.100	0.12	20.0	22.0	41.0
	82	110	2.5	0.12	14.4	0.08	80.0	0.08	0.750	0.22	77.0	73.0	122.0
						Chronic Cor Pulmonale							
Mean	52.0	86	2.31	0.096	10.56	0.05	51.7	0.046	0.475	0.157	60.7	67.3	52.0
S.D.			0.36	0.014	2.33	0.013	9.8	0.0095	0.152	0.022	8.7	6.0	11.5
Range	22	54	1.6	0.08	6.4	0.03	37.0	0.03	0.170	0.12	41.0	41.0	29.0
	68	110	3.0	0.12	15.6	0.08	67.0	0.09	0.770	0.22	75.0	75.0	81.0

Table II. *Correlation between normal peaked P wave and cardiac rates (average values)*

Cardiac rate (min.)	*Height (mm.)*	*Duration (sec.)*	*Surface area (mvs)*	*Rising time*		*Fall time*		*Rising velocity (mm./0.01 sec.)*	*P-R (sec.)*	*Macruz index*	*Angle°*		
				sec.	*%*	*sec.*	*%*				α	β	γ
51-60	1.06	0.095	4.99	.051	53.8	.044	46.4	0.220	0.168	1.30	41.9	46.6	91.5
61-70	1.03	0.095	4.91	.055	57.5	.040	42.5	0.182	0.158	1.50	39.8	46.1	94.1
71-80	1.31	0.102	6.60	.050	49.6	.052	50.5	0.289	0.159	1.79	46.6	51.8	81.6
81-90	1.42	0.096	6.77	.052	54.2	.044	45.9	0.283	0.152	1.71	45.9	55.6	78.5
91-100	1.26	0.093	5.82	.045	48.5	.048	51.5	0.306	0.158	1.43	45.1	52.7	82.2
101-110	1.43	0.093	6.72	.053	56.1	.040	43.6	0.283	0.163	1.32	45.0	55.2	79.8

magnitude of electrical potential produced during atrial activation, and the time interval required for its development, measured from the onset of the P wave up to its maximal expression, is called the rising time of the P wave. The average duration of the rising time in subjects with normal P waves measures 0.0512 second ± 0.0137; that represents 53.3 per cent ± 10.3 of the duration of the P wave. On the other hand, the rising time represents, geometrically, the length of the projection of the ascending limb of the P wave on its base line. Therefore, its relative duration indicates that the normal peaked P wave is built slightly asymmetrically because the projection of its peak on the base line is deviating to the left of the center by 3.3 per cent.

The rising velocity of the P wave expresses that height of this wave which arises during 0.01 second, supposing that velocity is constant. Rising velocity means a combined function of the atrial myocardium: its capacity to engender electrical potential and its conductivity. Normally the rising velocity measures 0.286 mm. per 0.01 second ± 0.111, which ranges from 0.10 to 0.75 mm. per 0.01 second.

In the present study the magnitudes of the angles of the atrial triangle were measured exactly. The reliability of this procedure could be demonstrated by duplicate measurements. In 50 cases a second measurement was performed at 20 to 30 days after the first determination. The average difference between the two measurements amounted to ± 3.2° (−5° to 8°).

The angular configuration of the normal peaked P wave was as follows. The ascending limb formed with the base line the angle α, which had a magnitude of 44° ± 9.6, with a range from 20° to 77°. The descending limb of the P wave returned to the base line, determining the angle β, which had an average magnitude of 51.5° ± 10.3, with a range from 22° to 73°. The apex of the P wave was formed by the angle γ, which had an average magnitude of 84.5° ± 19.7, with a range from 41° to 122°. Consequently, the normal peaked P wave was slightly asymmetrical because of the different magnitudes of angles α and β.

The influence of cardiac rates on these fundamental elements of the P wave cannot be definitely settled. The height of the P wave tends to increase with increasing cardiac rates. The duration of the P wave remains practically unaltered at different cardiac rates. Similarly, Shipley and Hallaran,[9] and Ashman and Hull[6] were unable to demonstrate any relationship between heart rate and duration of the P wave. The rising velocity shows a direct correlation with cardiac rates. Its average at low cardiac rates measured 0.201 mm. per 0.01 second, at medium cardiac rates 0.286 mm. per 0.01 second, and at high cardiac rates 0.295 mm. per 0.01 second.

The two basal angles of the atrial triangle tend to increase, and the apical angle to decrease with increasing cardiac rates. At low cardiac frequencies, angle α presents its smallest values: 41.9° and 39.5°. At moderate and fast cardiac rates it increases, exhibiting approximately identical values of 46° and 45°. The behavior of angle β is similar. The behavior of the apex angle is opposite to that of angles α and β.

Age definitely influences myocardial func-

tion and, therefore, the electrocardiogram. Simonson[10] states that age is the most important biologic variable of the normal electrocardiogram and is responsible for a large number of false diagnoses in older people. The present observations reveal that the height of the P wave decreases and its duration increases with advancing age.

Rising time and rising velocity of the P wave are defined as functional manifestations of the atrial myocardium and are clearly influenced by age: the rising time in the young age group averaged 0.0417 second (i.e., 45.7 per cent of the duration of the P wave); hence the projection of the peak of the atrial triangle fell to the right of its base, deviated from the center by 4.3 per cent. In the middle-aged group, rising time averaged 0.0469 second, 49.4 per cent of the duration of the P wave, so that in this group the peaked P wave was symmetrical, the projection of its peak falling on the center of its base. In the group of aged subjects (over 51 years old) the rising time was prolonged. Its average measured 0.0595 second, i.e., 60.9 per cent of the duration of the P wave. The projection of the peak of the P wave was markedly deviated to the left (10.9 per cent from the center). Influence of age on the shape of the P wave can thus be summarized as follows: the peaked P wave is symmetrical in middle-aged subjects, but asymmetrical with its peak deviated to the right in young subjects and to the left in older subjects.

Rising velocity presents the same dependence on age as voltage or conduction. In the subjects under 20 years of age, rising velocity averaged 0.31 mm.; in the middle-aged subjects it averaged 0.26 mm.; and in those over 51 years of age it decreased to an average of 0.20 mm. per 0.01 second. The progressive diminution of rising velocity of the normal P wave represents a hitherto undescribed manifestation of diminished functional capacity of the atrial muscle caused by aging.

There is a close correlation between the angular structure of the P wave and age. The average magnitude of angle α in the youngest age group was 48.7°, in the middle-aged group it was 45°, and in the old age group it exhibited its minimal magnitude of 41.9°. The behavior of angle β was similar. Angle γ, representing the angular magnitude of the apex, showed an opposite trend with increasing age. Measured in the young age group its average was 82.5°; in the middle-aged group it was 83.2°, and its maximal value of 86.9° was found in the old age group. Consequently, the angular elevation of the ascending limb of the peaked P wave decreases and the angular magnitude of the apex increases with age.

Right atrial overactivity was studied in a group of 30 patients suffering from chronic pulmonary disease (emphysema, chronic bronchitis, bronchial asthma). The height of the P wave measured 2.31 mm. ± 0.36, with a range from 1.6 to 3.0 mm. (an average increase of 86 per cent). Sano and associates[7] found in similar cases P waves that were 2.3 mm. in height; Zuckerman and associates,[11] in 50 cases of chronic cor pulmonale, measured 1.9 mm. (0.8 to 3.7 mm.), and Oliveira and Zimmerman,[12] 2.7 mm. (2.0 to 3.0 mm.). Duration of the P wave averaged 0.096 second ± 0.014, identical with normal findings. Rising time measured 0.05 second ± 0.013 (2.4 per cent shorter than the normal, representing 51.7 per cent of the duration of the P wave).

Table III. *Correlation between normal peaked P wave and age (average values)*

Age (yr.)	*Rate (min.)*	*Height (mm.)*	*Duration (sec.)*	*Surface area (mvs)*	*Rising time*		*Fall time*		*Rising velocity (mm./.01 sec.)*	*P-R (sec.)*	*Macruz index*	*Angle°*		
					sec.	*%*	*sec.*	*%*				α	β	γ
<20	80.5	1.32	0.0858	5.58	.041	45.7	.044	54.3	0.31	0.149	1.36	48.7	48.8	82.5
21-50	80.3	1.26	0.0943	5.92	.046	49.4	.047	50.6	0.26	0.153	1.38	45.0	51.8	83.2
>51	79.5	1.22	0.0998	6.07	.059	60.9	.040	39.1	0.20	0.164	1.54	41.9	51.2	86.9

Table IV. *Acute P pulmonale produced by breathing against manometric pressure*

Number		Rate (min.)	Height (mm.)	Duration (sec.)	Surface area (mvs)	Rising time		Fall time		Rising velocity (mm./.01 sec.)	P-R (sec.)	Macruz index	Angle°		
						sec.	%	sec.	%				α	β	γ
1.	Rest	75	1.6	0.12	9.6	Rounded		Rounded			0.20	1.50	43	61	76
	EE	107	4.0	0.08	16.0	.05	63	.03	37	0.80	0.14	1.33	78	76	26
2.	Rest	71	1.0	0.10	5.0	Rounded					0.16	1.66	55	64	61
	EE	107	3.2	0.08	12.8	.06	75	.02	25	0.53	0.12	2.00	60	83	37
3.	Rest	78	1.0	0.08	4.0	Rounded					0.18	0.80	42	70	68
	EE	125	2.4	0.10	12.0	.08	80	.02	20	0.30	0.14	2.50	46	75	59
4.	Rest	83	1.4	0.11	7.7	Rounded					0.17	1.83	48	65	67
	EE	128	3.0	0.10	15.0	.07	70	.03	30	0.43	0.14	2.50	60	72	48
5.	Rest	69	1.4	0.09	6.3	.04	45	.05	55	0.35	0.15	1.50	58	66	56
	EE	107	2.5	0.08	10.0	.06	75	.02	25	0.42	0.14	1.33	61	73	46
6.	Rest	90	1.2	0.11	6.0	Rounded					0.15	2.75	38	53	89
	EE	120	2.2	0.10	11.0	.06	60	.04	40	0.37	0.14	2.50	58	62	60
7.	Rest	83	1.0	0.11	5.5	.06	55	.05	45	0.17	0.15	2.75	45	45	90
	EE	125	2.0	0.10	10.0	.06	60	.04	40	0.33	0.14	2.50	61	62	57
8.	Rest	68	2.0	0.10	10.0	Rounded					0.16	1.66	68	64	48
	EE	111	4.0	0.08	16.0	.05	63	.03	37	0.80	0.12	2.00	77	78	25
9.	Rest	63	1.0	0.08	4.0	Rounded					0.15	1.14	56	73	51
	EE	82	2.0	0.08	8.0	.05	63	.03	37	0.40	0.12	2.00	65	75	40
10.	Rest	62	1.2	0.09	5.4	.04	45	.05	55	0.30	0.16	1.29	55	57	68
	EE	104	2.0	0.08	8.0	.05	63	.03	37	0.40	0.15	1.14	60	69	51
11.	Rest	66	0.8	0.10	4.0	Rounded					0.16	1.66	42	56	82
	EE	100	2.6	0.10	13.0	.06	60	.04	40	0.43	0.15	2.00	53	71	56
12.	Rest	85	1.0	0.10	5.0	Rounded					0.14	2.50	45	58	77
	EE	125	1.5	0.08	6.0	.06	75	.02	25	0.25	0.12	2.00	38	76	66
13.	Rest	69	1.2	0.09	5.4	.04	45	.05	55	0.30	0.16	1.29	40	52	88
	EE	107	3.0	0.08	12.0	.05	63	.03	37	0.60	0.12	2.00	62	73	45
14.	Rest	69	1.4	0.09	6.3	.04	45	.05	55	0.35	0.16	1.29	50	58	72
	EE	96	3.5	0.08	14.0	.05	63	.03	37	0.70	0.12	2.00	74	76	30
15.	Rest	71	1.2	0.10	6.0	.06	60	.04	40	0.20	0.16	1.66	35	60	85
	EE	97	3.0	0.08	12.0	.05	63	.03	37	0.60	0.12	2.00	49	68	63

EE: Expiratory effort.

According to the geometrical significance of the rising time the pulmonary P wave is traced almost symmetrically, because projection of its peak deviates from the center to the left of the base line only by 1.7 per cent. The rising velocity was 0.475 mm. per 0.01 second ± 0.152 (0.17 to 0.77 mm. per 0.01 second), corresponding to an increase of 82 per cent.

The basal angles of the pulmonary P wave are wider than normal. Angle α measured 60.7° ± 8.7 (increased by 37.9 per cent), and angle β was 67.3° ± 6.0 (increased by 30 per cent). The angle γ of the apex was decreased (on an average, 52.0° ± 11.5), indicating a diminution of 38.5 per cent.

Bürger,[13] in 1926, investigated the electrocardiographic changes that appear during expiratory effort (experiment of Valsalva) during breathing against manometric pressure. This author observed increased height of the P wave in every case. This method was employed to investigate the morphologic particularities of experimentally produced acute pulmonale P wave.

Breathing against manometric pressure produced the tallest of all the P waves examined. The average height was 2.73 mm., 120 per cent greater than our average normal standard, with ranges from 1.5 to 4.0 mm. The average duration measured 0.0866 second; the shortest and the average surface area was 11.72 mvs, the largest of all cases studied. Rising time averaged 0.0573 second, prolonged by 12 per cent as compared with the normal standard, representing 66.4 per cent of the duration of the

P wave. Both figures indicate that the projection of the peak on the base of the atrial triangle is eccentric, deviating from the center to the left by 16.4 per cent, and that the trigonometric structure of the atrial triangle is most asymmetrical. The average rising velocity was 0.49 mm. per 0.01 second, 104 per cent greater than in normal cases. Measurement of the angular magnitude of this experimentally produced acute P pulmonale confirmed its skewness. Angle α measured 60.1°, and angle β 72.6°; the average difference between the two basal angles was 12.5°, 60 per cent greater than in normal cases. Angle γ was the most diminished, measuring 47.3°, i.e., 44 per cent less than the normal average. The marked diminution of angle γ is apparent on simple inspection.

The exact mechanism of production of the electrocardiographic pattern of pulmonary P is unknown. Positional changes, more vertically directed P vector, increase of muscle mass with or without enlargement of the right auricular cavity, and increased sympathetic nervous tone are frequently present. Low oxygen saturation of the arterial blood plays a predominant role. However, in some cases the pulmonary P pattern can clearly be observed in the absence of any atrial abnormality (Mack and Snider[14]).

Experiences with the Macruz index. Macruz and associates[4] formulated simple quantitative criteria based on the conventional electrocardiogram for the recognition of right and left atrial enlargement. According to these authors, in normal conditions the duration of the P wave related to the duration of the P-R segment is relatively constant, presenting an average value of 1.2, with ranges from 1.0 to 1.6. In cases of right atrial enlargement the duration of the P wave remains unaltered but the P-R interval increases, so that the ratio of P to P-R segment falls below the normal range. On the other hand, left atrial enlargement causes an increase in the duration of the P wave and a shortened P-R segment, and, consequently, the ratio of P to P-R segment rises above the normal limit of 1.6. This simple test has been widely used in recent years and has been intensively investigated in the present study.

Our experiences differed from those reported by Macruz and collaborators. In 180 normal records the average ratio was 1.52, which figure agrees with that of the authors mentioned, but the ranges were extremely wide, varying from 0.7 to 5.0. Distribution was as follows: less than 1.0, indicating right atrial enlargement, was observed in 30 cases (16.7 per cent); normal values of 1.1 to 1.6 were present in 65 cases (36.1 per cent), and greater than normal values were observed, indicating left atrial enlargement in 85 cases (47.2 per cent). Greater than normal ratios were observed in the following order: 1.7 to 2.0 in 45 cases (25.0 per cent); 2.1 to 3.0 in 33 cases (18.3 per cent); 3.1 to 4.0 in 4 cases (2.2 per cent); and 4.1 to 5.0 in 3 cases (1.7 per cent). Consequently, in perfectly healthy individuals the Macruz criteria are concordant with normalcy in 36.1 per cent only, whereas they indicate abnormal conditions of the atria (sometimes very pronounced) in 63.9 per cent of these cases.

Macruz and associates state that cardiac rates exert no significant effect on the magnitude of the ratio. According to our experience, the index of Macruz gives a maximum value of 1.79, slightly higher than the upper normal limit at medium cardiac frequencies of 71-90, whereas its average decreases at slower as much as at faster cardiac rates.

In cases of chronic cor pulmonale the index of Macruz averaged 1.57, with ranges from 0.8 to 3.3. These figures are identical with those which we have observed in the group of normal subjects, and, thus, the formulated ratio with its value of less than 1.0 was missed.

In 15 cases, transient acute right atrial overload was produced by breathing against manometric pressure. In these cases, and during rest, the ratio was 1.56 (0.8-2.5). During forced respiration the ratio increased to 1.98 (+27 per cent), which is a paradoxical reaction. This difference, however, is not statistically significant. The standard error of the mean ratio in rest, determined by the formula $\sqrt{\frac{\Sigma\,(\delta^2)}{n\,(n-1)}}$, was 0.147, and, thus, differences up to 3 S.E.M. 0.441 are of no statistical significance. The ratio increased during expiratory effort by 0.420, that is, less than

3 S.E.M., which is also not significant. In conclusion, we may state that the criteria evolved by Macruz and associates to indicate right or left atrial enlargement are diagnostically unreliable, first, because normal variants are extraordinarily wide, and, secondly, because changes in the ratio do not follow truly the observed functional and electrocardiographic alterations of the atria.

The quantitative study of the P wave as outlined in the present paper cannot, unfortunately, be used for changes of the P wave in the opposite direction, i.e., when its size decreases. Reduced magnitudes, even of the normal P wave, make it desirable to increase the sensitivity of the recording (in order to obtain greater deflections) and to increase the speed (in order to widen time intervals), as suggested by Abildskov.[3] Measurement of P waves with abnormally low deflections by means of the current method of recording is inaccurate and, so, unsuitable.

Summary

1. The P wave, specifically the peaked-form variety, was studied in normal individuals, in subjects with cor pulmonale, and in those with acute experimental pulmonale P pattern produced by breathing against manometric pressure.

2. In addition to the conventional data, some new functional criteria, such as rising time and rising velocity, were investigated. The angular structure of the atrial triangle was examined and the standard values established.

3. The correlation between the linear and angular structure of the atrial wave and cardiac rate and age was established exactly.

4. The index of Macruz was critically examined in light of the conditions described, and its diagnostic value assessed.

5. The methods of investigation herein described increase the diagnostic value of the conventional electrocardiogram with respect to the atrial wave.

Addendum

Since the preparation of this paper, Kahn and associates[15] have published a report in which they conclude that the ratio of Macruz is not a reliable test of atrial enlargement.

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Kinetocardiographic findings in patients with congestive heart failure and changes after therapeutic digitalization

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Recent work done in this laboratory[1] described alterations in precordial movements during anginal attacks and the effect of therapeutic doses of glyceryl trinitrate on these abnormal deflections. These observations have been confirmed and evidence introduced that transient failure occurs at the time of anginal pain in some patients,[2] a finding noted previously by Müller and Rorvik[3] during right heart catheterization.

The purpose of this communication is to report abnormalities in tracings of precordial motions in patients with evidence of congestive heart failure, the changes produced by therapeutic digitalization, and, in a few instances, digitalis intoxication.

Methods

Low - frequency precordial movements (kinetocardiograms; KCG) were recorded by the bellows-crossbar technique as previously described.[4] The same terminology is used as before; i.e., K_1 represents tracings recorded from the right parasternal line (V_1), K_2 from the vertical line corresponding to the V_2 lead of the ECG, etc. A second numeral in the subscript indicates the intercostal space from which the record was taken; i.e., a K_{45} tracing is one from the right parasternal line in the fifth intercostal space.

The K_1 through the K_4 areas were studied; however, findings from the K_1 and K_2 positions were the most striking and consistent and are the ones reported. The areas studied were marked on each patient with an indelible solution to aid in reproducible placement of the bellows with successive tracings.

Five movements are considered (Fig. 1). Those recorded after atrial excitation and before ventricular excitation are due to atrial activity,[5] and two have been chosen for study: an initial outward deflection termed the "atrial upstroke" (AU), and a second inward motion referred to as the "atrial downstroke" (AD). When no distinct separation of passive ventricular filling (VF) and atrial upstroke deflections occurred, the AU value could not be determined.

The major inward (downward) deflections recorded at the K_2 area after the onset of Q of the ECG is attributed to change of volume as the ventricles eject.[6] This motion is constantly present in normal subjects and is the largest deflection associated with ventricular systole at this area; it will be referred to as the "ventricular ejection downstroke" (EDS).

A mid-systolic outward movement (MOM) and a motion previously attributed[6] to passive ventricular filling (VF) are reported.

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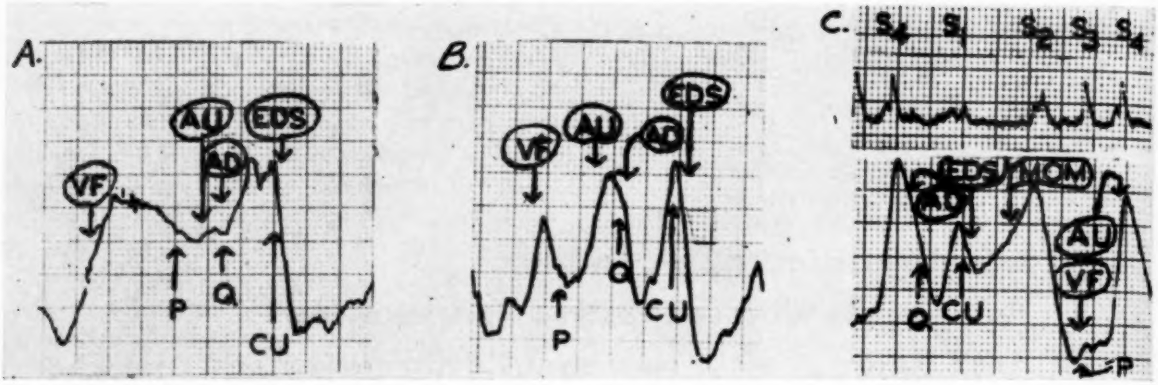

Fig. *1*. Paper speed, 50 mm./sec. Tracings begin and end in diastole so as to better demonstrate changes in passive filling and atrial contraction. The characteristic movements in a normal subject (*A*), a patient with predominant left ventricular failure (*B*), and a patient with biventricular failure (*C*) are shown. *A*, Note the small atrial upstroke movement (*A U*) occurring after the P wave of the ECG, and the ventricular ejection downstroke motion (*EDS*) which occupies a major portion of the total amplitude of the complex. The ventricular filling wave (*VF*) is quite prominent. *B*, The atrial upstroke motion (*A U*) is markedly increased, and the passive ventricular filling wave (*VF*) decreased. The ventricular ejection downstroke (*EDS*) continues to constitute a major portion of the total amplitude of the entire complex. *C*, The atrial upstroke motion occupies a major portion of the total amplitude of the entire complex. The ventricular ejection downstroke (*EDS*) is markedly decreased, and the ventricular filling wave is quite small. A mid-systolic outward movement (*MOM*) is now present. Note the absence of this latter movement in records *A* and *B*. A definite separation of ventricular filling and atrial upstroke motions exists. The rectified heart sound recordings demonstrate both a protodiastolic gallop (S_3) and an atrial gallop (S_4); the former is correlated with the tiny ventricular filling wave (*VF*), and the latter with the prominent atrial upstroke motion (*AU*). *AD:* Atrial downstroke. *TA:* Total amplitude. *P:* P wave of ECG. *Q:* Q wave of ECG. *CU:* Carotid upstroke. *VF:* Passive ventricular filling. All sounds rectified: S_1, S_2, S_3, S_4: First, second, and third heart sounds, and fourth (atrial) sound, respectively.

To determine more accurately the serial changes in the kinetocardiograms as treatment for congestive failure progressed, the amplitudes of the atrial and ventricular movements were expressed as a percentage of total amplitude of the complete cardiac cycle complex. Total amplitude (TA) was determined by measuring the distance from the highest to the lowest point of a given cardiac cycle (Fig. 1). Five percentages were calculated, indicating the following relationships: AU/TA × 100, AD/TA × 100, EDS/TA × 100, AU/EDS × 100, and AD/EDS × 100.

Patients

Before the study of patients with congestive heart failure was undertaken, the effects of digitalis on the KCG of 6 normal persons were first determined. Fourteen patients were then studied. Six had clinical evidence of predominant left ventricular failure, and 8 displayed biventricular failure. Table I shows the clinical and objective evidence for cardiac decompensation in each. Twelve had never received any form of treatment for failure prior to the study; 2 had received both diuretics and digitalis in the past but were essentially undigitalized, since marked improvement followed large doses of the drug. Serial records were obtained on each during the digitalizing process.

Results

Fig. 2 illustrates the reproducibility of the records and shows four consecutive daily tracings from the K_2 area taken at the same sensitivity from a normal man. No significant variability occurred from day to day in relative amplitudes of atrial or ventricular motions.

The 6 normal subjects exhibited no significant change in the KCG after digitalization (Fig. 3).

Atrial movements. Previous studies[7] in normal subjects of various ages have shown that the atrial upstroke movement does not exceed 27 per cent of total amplitude. In a series of normal subjects who were over 35 years of age the mean percentage atrial downstroke (AD) of total complex excursion was 21, with only one value in excess of 27.

Table II shows values for the two atrial movements before and after digitalization.

No untreated patient had an AU/TA value of less than 37 per cent (mean, 47 per cent) or an AD/TA percentage of less than 20 per cent (mean, 38 per cent). The means after maximum doses of digitalis were 18.5 and 18.1 per cent, respectively. Each subject showed a decrease in these relative percentages as treatment progressed (Figs. 7 and 8).

The atrial downstroke percentage (AD/TA × 100) showed a wide scatter (Fig. 4) before treatment; 5 patients, 4 of whom were suffering from biventricular failure, had high percentages. After therapy, values were within upper limits of those established for normal.

Ventricular ejection downstroke. The range for this movement at the K_2 area was wide in both normal subjects and patients with untreated failure (Fig. 4). Those with predominant left ventricular failure had essentially the same means before and after digitalization (77 and 87 per cent, respectively), whereas all with biventricular failure had values below 30 per cent; one showed a value below 30 per cent after digitalization.

Ratio of atrial movements to ventricular ejection downstroke. The AU/EDS ratio ranged from 48 to 1,400 per cent (median, 87 per cent) before treatment and 17 to 58 per cent after digitalization. Those with biventricular failure had values in excess of 100 per cent (146 to 1,400 per cent), whereas those with primarily left ventricular failure showed a range of 48 to 87 per cent. The two highest values after therapy, 45 and 58 per cent, were from

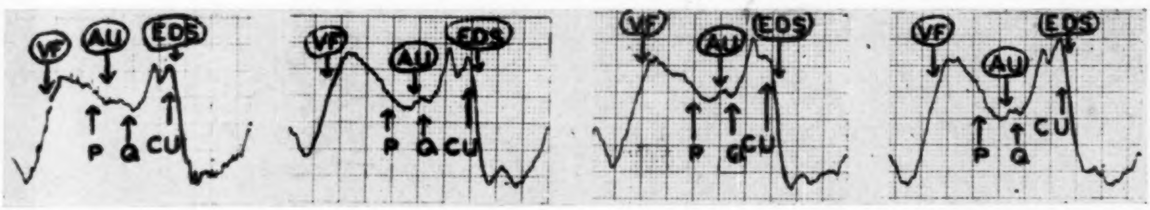

Fig. 2. This figure shows the reproducibility of records obtained from a normal 24-year-old man over four consecutive days from one area, the left parasternal line in the fifth intercostal space (K_{25}). Each tracing begins and ends with the carotid incisural notch and represents one complete cardiac cycle. Time lines are 0.02 second. The recording apparatus was calibrated before each tracing was made, in order to assure the same sensitivity for each tracing obtained. The subject was marked with an indelible solution to aid application of the bellows at the same point each time. Note the reproducibility seen in both configuration and amplitude. No appreciable variation in atrial movements or ventricular ejection movements is seen. *P:* P wave of ECG. *Q:* Q wave of ECG. *CU:* Carotid upstroke. *AU:* Atrial upstroke. *EDS:* Ventricular ejection downstroke. *VF:* Passive ventricular filling wave.

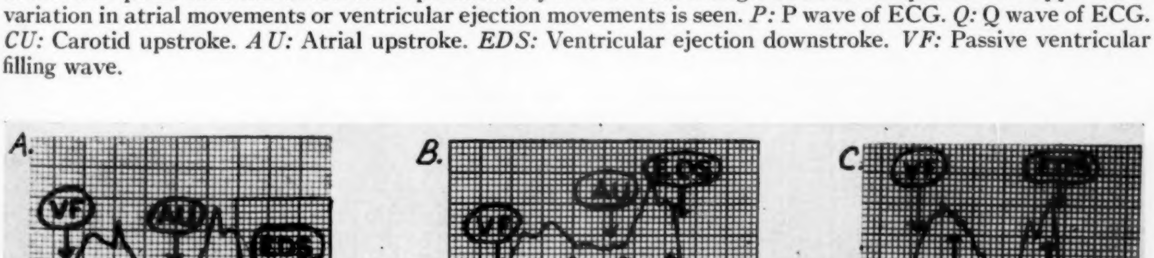

Fig. 3. This figure shows the effect of digitalis on kinetocardiograms taken from a normal subject. All records begin and end with the carotid incisural notch, and are from the left parasternal line, fifth intercostal space (K_{25}). Time lines are 0.02 second. *A,* Control record. *B,* After 10 mg. of gitalin (2 mg./day for 5 days). *C,* Eight days after withdrawal of digitalis. The control record, the tracing taken after ingestion of 10 mg. of gitalin, and the recording made 8 days after withdrawal of the drug show no essential differences. Clinically, the only effect noticed was a varying degree of malaise. When this figure is compared to Fig. 8, the marked effect of digitalis on the failing heart as reflected by the KCG is clearly seen. *P:* P wave of ECG. *Q:* Q wave of ECG. *CU:* Carotid upstroke. *AU:* Atrial upstroke. *EDS:* Ventricular ejection downstroke. *VF:* Passive ventricular filling.

Table I. Summary of data on patients studied

Patient	Sex	Age (yr.)	Type of congestive heart failure*	Diagnosis	Evidence for heart failure: Dyspnea		Edema	Orthopnea	PND†	Circulation time‡ (sec.)	Vital capacity (L.)		Loss of weight after digitalization (lb.)	Digitalis preparation used	Diuretics used
					Effort	Rest					Before digitalization	After digitalization			
1. Q.F.	F	59	BVF	HCVD CAD	Yes	No	Minimal	No	No	31	2.0	2.8	9	Gitalin	No
2. H.A.	M	59	BVF	HCVD	Yes	Yes	Anasarca	Yes	Yes	58	2.0	3.2	25	Gitalin	No
3. M.S.T.	F	55	BVF	CAD	Yes	Yes	Moderate, with hydrothorax	Yes	Yes	24	1.0	1.8	16	Gitalin	No
4. O.D.	F	67	BVF	AI	Yes	Yes	Anasarca	Yes	Yes	—	1.0	—	89	Digoxin	Yes
5. W.H.	M	48	BVF	AI	Yes	Yes	Moderate, with hydrothorax	Yes	Yes	29	1.0	2.2	16	Gitalin	No
6. J.M.	M	26	BVF	AI	Yes	Yes	Moderate, with ascites	Yes	Yes	36	2.8	3.4	4	Gitalin	No
7. J.W.	M	60	BVF	AI	Yes	Yes	Moderate	Yes	Yes	28	2.0	3.8	9	Gitalin	Yes
8. L.S.	M	62	LVF	CAD	Yes	No	No	No	—	23	3.8	3.8	0	Gitalin	No
9. W.M.	M	58	LVF	CAD	Yes	Yes	No	No	Yes	—	4.5	—	0	Gitalin	No
10. H.W.	M	55	LVF	CAD	Yes	No	No	No	Yes	—	4.5	—	0	Gitalin	No
11. W.N.	F	70	LVF	CAD	Yes	No	No	Yes	Yes	—	1.6	2.2	0	Gitalin	No
12. W.K.	M	51	LVF	AI	Yes	Yes	No	Yes	Yes	—	1.2	2.8	0	Gitalin	No
13. L.P.	M	64	LVF	AI	No	Yes	No	No	Yes	—	1.8	2.8	5	Gitalin	No

*BVF: Biventricular failure. LVF: Left ventricular failure only.
†PND: Paroxysmal nocturnal dyspnea.
‡Arm-to-tongue circulation time.
HCVD: Hypertensive cardiovascular disease.
CAD: Coronary artery disease. AI: Aortic insufficiency.

Table II. *Percentages of the parameters studied in patients with congestive heart failure before and after digitalization*

Patient	*AU/TA × 100*		*AD/TA × 100*		*EDS/TA × 100*		*AU/EDS × 100*		*AD/EDS × 100*		*Type of cardiac failure‡*
	Before digitalization	*After digitalization*	*Before digitalization*	*After digitalization*	*Before digitalization*	*After digitalization*	*Before digitalization*	*After digitalization*	*Before digitalization*	*After digitalization*	
1. Q.F.	47*	20	43	25	29	90	150*	22	90	33	B
2. W.H.	40	15	—	—	3	61	1,400	25	—	—	B
3. M.S.T.	—	—	60*	27	0	17	—	—	175*	60	B
4. O.D.	42	15	26	5	29	45	146	33	175	20	B
5. H.A.	—	—	55	12	10	71	—	—	1,100	17	B
6. J.M.	45	22	62	27	27	37	167	58	186	29	B
7. J.W.	75	14	25	27	45	31	167	45	50	86	B
8. L.W.S.	37	26	29	10	56	90	65	29	70	24	L
9. W.M.	53	20	20	17†	100	91	53	22	28	17†	L
10. W.N.	43	16	27	21	50	81	87	19	38	21	L
11. H.W.	42	14	45	22	88	83	48	17	56	31	L
12. L.P.	55	27	—	—	93	100	59	27	—	—	L
13. W.K.	40	14	25	6	74	79	54	17	31	10	L

*Values obtained 1 day after digitalization was begun.
†Values obtained 1 day before digitalization was completed.
‡B: Biventicular failure patients. L: Patients with left ventricular failure only.
AU: Atrial upstroke amplitude. AD: Atrial downstroke amplitude. TA: Total amplitude of the complex. EDS: Ventricular ejection downstroke amplitude. Values for AU and EDS were obtained from the K_2 area. Values for AD were obtained from the K_1 area.

Table III. *Effect of digitalis intoxication on kinetocardiograms*

Patient	*AU/TA × 100*			*AD/TA × 100*			*EDS/TA × 100*			*AU/EDS × 100*			*AD/EDS × 100*		
	Before digitalization	*After digitalization*	*Digitalis intoxication*	*Before digitalization*	*After digitalization*	*Digitalis intoxication*	*Before digitalization*	*After digitalization*	*Digitalis intoxication*	*Before digitalization*	*After digitalization*	*Digitalis intoxication*	*Before digitalization*	*After digitalization*	*Digitalis intoxication*
W.K.	40	15	50	25	17	53	74	79	65	54	17	77	35	22	82
L.W.S.	54	28	44	29	22	41	42	91	74	130	31	60	70	24	58
M.S.T.	—	—	—	97	34	34	0	17	3	—	—	—	2,400	200	1,200

AU: Atrial upstroke amplitude. AD: Atrial downstroke amplitude. TA: Total amplitude of the complex. EDS: Ventricular ejection downstroke amplitude.

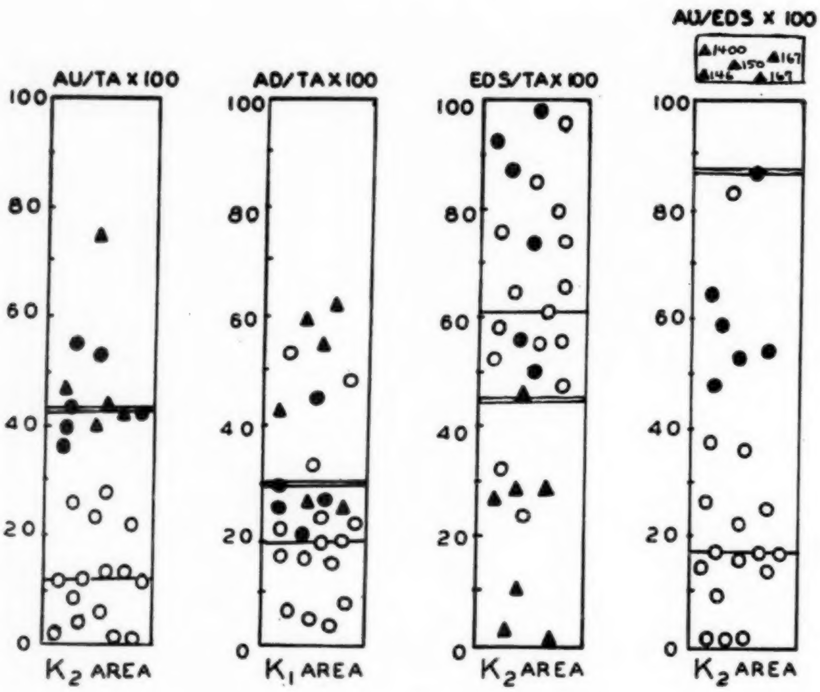

Fig. *4*. This figure shows a comparison of the various parameters studied in normal subjects and in patients with untreated cardiac failure. Left to right: *A-D*. *A*, Atrial upstroke motion. A clear separation of normal subjects and patients with failure occurs. The median for the normal subjects is 12 per cent, and the median for the untreated patients with cardiac failure is 44 per cent. *B*, Atrial downstroke motion. The difference in medians between the normal subjects and patients with untreated failure is apparent; however, a considerable degree of overlap exists as regards distribution of values. *C*, Ventricular ejection downstroke motion. Little overlapping occurs with the two types of patients studied. The 5 patients who show values below 30 per cent were those with biventricular failure, and the 6 with values of 50 per cent or greater had clinical evidence of left ventricular failure only. Three of the 16 normal subjects exhibited values below 50 per cent, with only one below 30 per cent. *D*, Ratio of atrial upstroke amplitude to ventricular ejection downstroke amplitude. Very little overlap occurs; the difference in medians is quite marked. Five of the untreated patients had values above 100 per cent; only one normal subject had a value in excess of 37 per cent. White circles: Normal subjects. Black circles: Untreated patients with predominant left ventricular failure. Black triangles: Untreated patients with biventricular failure. Double horizontal rules: Median for all patients. Single horizontal rules: Median for normal subjects. *AU:* Atrial upstroke. *AD:* Atrial downstroke. *EDS:* Ejection downstroke (ventricular). *TA:* Total amplitude.

subjects with long-standing biventricular failure.

The range of the AD/EDS percentage in untreated patients was 28 to 100 per cent; after therapeutic digitalization it was 10 to 86 per cent, and two values were above 33 per cent.

The changes noted in each patient before and after digitalization are presented in Table II and Figs. 5 and 6.

Ventricular mid-systolic movement. An exaggerated mid-systolic movement was present at the K_2 area in all patients with untreated biventricular failure. The effect of digitalis on this is shown in Fig. 8. After maximal digitalization this motion disappeared in 4 of 7 subjects, markedly decreased in 2, and failed to show any change in 1.

Changes in serial kinetocardiograms. All patients showed a progressive decrease in atrial motions while being digitalized. Fig. 7 demonstrates the results obtained over 5 consecutive days, from the untreated state to full digitalization, in a patient suffering from failure of both ventricles. This was representative of all patients and was correlated with more classic objective evidence of improvement (decreased severity of symptoms, increased vital capacity, decreased circulation time, etc.).

The actual complexes from which data for Fig. 7 were derived are shown in Fig. 8. A marked reduction in atrial deflections was seen 18 hours after oral digitalis therapy was begun, a time at which minimal increase in the ventricular ejection downstroke occurred. When the latter movement did show early accentuation, it was only in those patients with failure of short duration.

In the tracing shown in Fig. 8 the midsystolic outward movement progressively decreased as digitalization became complete, and disappeared entirely 3 days after the drug was started.

Every patient showed an increase in the amplitude of the passive ventricular filling wave as treatment with digitalis progressed; this was concomitant with the decrease in atrial deflections.

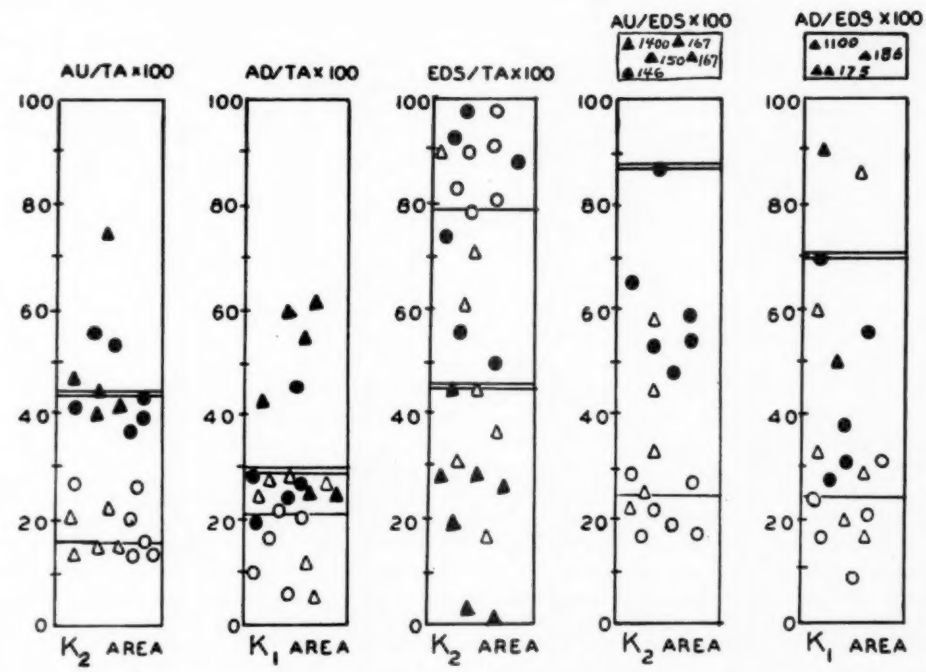

Fig. 5. This figure shows percentage values for the five parameters studied before and after therapeutic digitalization. Left to right: *A-E*. *A*, Atrial upstroke motion. The median for this movement fell from 44 per cent (range, 37 to 75 per cent) before digitalis therapy to 17.5 per cent after full digitalization (range, 14 to 27 per cent). *B*, Atrial downstroke motion. This ranged from 20 to 62 per cent (median, 28 per cent) before digitalization, and 5 to 27 per cent (median, 22 per cent) after digitalization. All showed a decrease in relative amplitude of this movement after therapy. *C*, Ventricular ejection downstroke motion. The medians before and after digitalization are 45 (range, 0 to 100) and 79 per cent (range, 17 to 100 per cent), respectively. Five patients, all with biventricular failure, had values below 30 per cent before digitalization, and only one had less than 30 per cent after maximum doses of the drug, this one being studied after long-standing, severe biventricular failure. The scatter here is so marked that no significance can be attached to this determination as regards the group of patients studied; however, changes in individual patients indicated a trend toward significant increases after digitalization, especially in the patients with biventricular failure. *D*, Comparison of atrial upstroke amplitude to ventricular ejection downstroke amplitude. This ranges from 48 to 1,400 per cent (median, 88 per cent) before therapy was begun, and 17 to 58 per cent (median, 25 per cent) after full digitalization. The values over 100 per cent observed before treatment were seen only in those patients with clinical evidence of biventricular failure. Only 2 patients had values in excess of 35 per cent after digitalization, and both had been in biventricular failure of long duration. *E*, Atrial downstroke amplitude to ventricular ejection downstroke amplitude. The predigitalization median for this parameter was 70 per cent (range, 28 to 1,100 per cent), and the post-digitalization median was 24 per cent (range, 10 to 86 per cent). The highest values recorded after maximal drug dosage were from those with prolonged and severe biventricular failure. Black triangles: Untreated patients with biventricular failure (BVF) before digitalization. White triangles: After digitalization (BVF). Black circles: Untreated patients with left ventricular failure (LVF) before digitalization. White circles: After digitalization (LVF). Double horizontal rules: Median before digitalization. Single horizontal rules: Median after digitalization. *AU:* Atrial upstroke. *EDS:* Ventricular ejection downstroke. *AD:* Atrial downstroke. *TA*: Total amplitude.

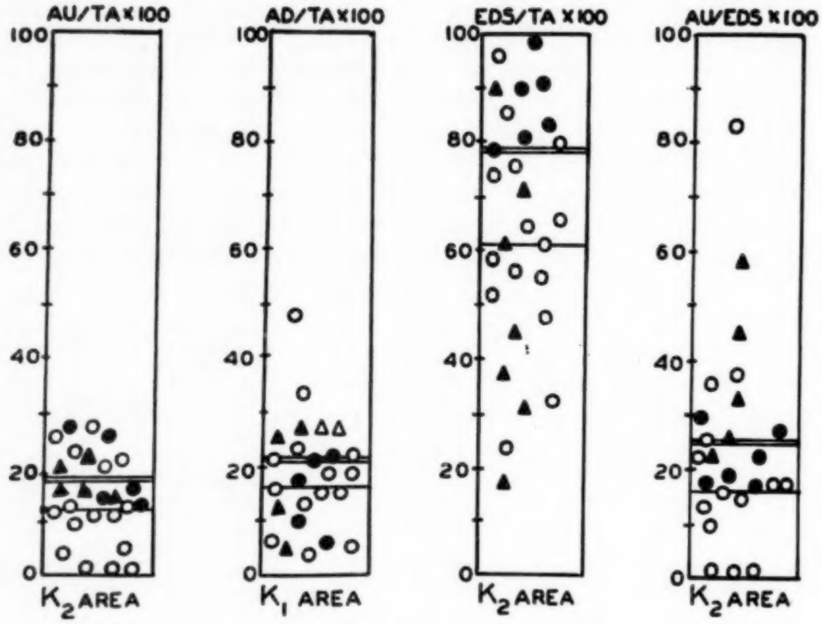

Fig. *6*. This figure shows a comparison of normal subjects and fully digitalized patients who have improved from congestive heart failure. Left to right: *A-D*. *A*, Atrial upstroke motion. The median for both normal subjects and digitalized, improved patients with failure is approximately the same; the range for the treated patients falls within that for normal subjects. *B*, Atrial downstroke motion. Again, values for both normal subjects and fully digitalized patients are almost identical. *C*, Ventricular ejection downstroke. The scatter is so marked that no significance can be attached to it; the range, however, is almost identical for both groups. *D*, Atrial upstroke amplitude to ejection downstroke amplitude. Medians for the two types of subjects are almost identical. All treated patients with failure fell within the range for normal subjects. Fully digitalized patients improved from heart failure: black triangles = biventricular failure; black circles = predominant left ventricular failure only. White circles = normal subjects. Double horizontal rules: Median for patients. Single horizontal rules: Median for normal subjects. *AU:* Atrial upstroke. *AD:* Atrial downstroke *EDS:* Ventricular ejection downstroke. *TA:* Total amplitude.

Effect of intravenous digitalis on the kinetocardiogram. One patient who was taking oral digitalis but was underdigitalized and had obvious biventricular failure was given a total of 0.4 mg. of lanatoside-C intravenously after a series of control records were obtained. In 2 hours, a decrease in the atrial upstroke, increase in ejection downstroke, and decrease in percentage AU/EDS were observed (Fig. 9). An increase in the passive ventricular filling wave was also noted. These changes were similar to those produced by slow oral digitalization.

The kinetocardiographic changes with clinical evidence of digitalis intoxication. Of 9 patients with digitalis intoxication, 6 had gastrointestinal manifestations only, and these for a brief period. These patients exhibited no changes due to excessive amounts of the drug from records taken shortly before. However, 3 had evidence of severe intoxication of several hours' duration, and 2 showed cardiac changes (ECG; increased severity of failure). These 3 displayed kinetocardiographic changes comparable to those obtained during the untreated state. Table III shows the parameters studied before treatment, at the time of maximal digitalis response, and after ingestion of excessive amounts of the drug. Fig. 10 shows complexes at various levels of management.

Discussion

All patients with heart failure exhibited alterations in ventricular filling manifested by reduced passive ventricular filling waves and exaggerated movements associated with atrial contraction. Patients with biventricular failure displayed two additional changes which were not present in patients with left ventricular failure alone. These changes

were decreased inward motions associated with rapid ventricular ejection and increased mid-systolic outward deflections.

The decreased passive ventricular filling waves and increased atrial movements are presumably the result of a decrease in ventricular contractility,[8,9] leading to defective emptying, increase in residual volume, increase in ventricular diastolic pressure, and usually a decrease in stroke volume.[10,11] This leads to distention of the ventricle, and thus atrial distention; consequently, the atrium contracts with more vigor and an increase in amplitude of recorded atrial movements occurs. Ventricular filling is thus accomplished more by atrial contraction and less by passive inflow, since rapid equalization of pressures between the atrium and ventricle occurs with the latter. Therefore, the passive ventricular filling wave, as recorded by the kinetocardiogram, is reduced in amplitude.

These findings as regards *atrial motions* are in agreement with those of Dock.[12] The discrepancy of this work with that of Dock[12] and Heyer[13] as related to the *passive ventricular filling wave* is more apparent than real. Heyer, using the electrokymogram, found the duration of passive filling to be shorter in patients with congestive heart failure, and Dock, using the ballistocardiogram, found large protodiastolic movements in such patients. The former work points toward rapid equalization of pressures between atrium and ventricle by small volumes of blood entering an already distended ventricle; the latter work points toward increased force of blood moving into the ventricles during early diastole. Thus, it would appear that during congestive failure the force of early filling is augmented even though the volume is diminished.

When patients with left-sided failure only were compared with those who had defective action of both ventricles, certain similarities and certain differences were noted. Both groups exhibited exaggerated atrial and decreased passive filling motions. However, the ejection downstroke, which is probably related to the output during rapid emptying, was different in the two groups, being essentially normal when only the left ventricle was at fault but sharply decreased when right ventricular failure was also present. The explanation for this observation is possibly related to the differences in the architecture and pressure-volume relationships of the two chambers. In the thick-walled left ventricle, a small rise in diastolic volume will lead to a large increase in pressure and, hence, to pulmonary congestion. However, the signs of right-sided failure, being related to a rise in pressure in this more distensible chamber, will occur only after a relatively large amount of residual blood has accumulated. Thus, the congestive manifestations occur early in relation to the degree of dilatation in the case of the left ventricle and at a time when this chamber is still able to maintain a relatively normal resting output. The reverse is true of the right ventricle.

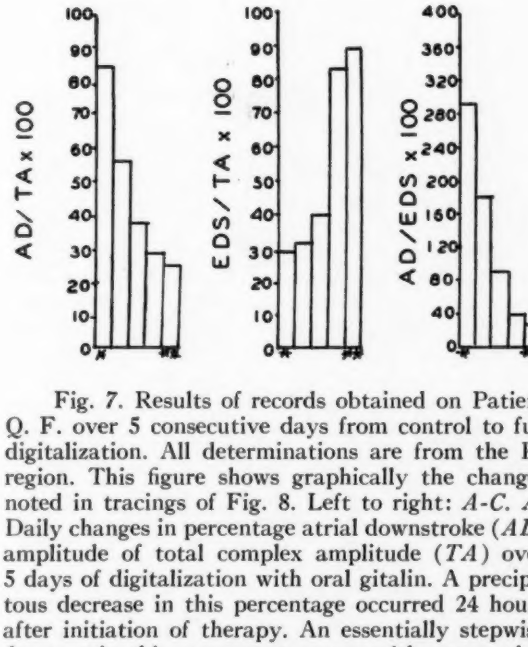

Fig. 7. Results of records obtained on Patient Q. F. over 5 consecutive days from control to full digitalization. All determinations are from the K_2 region. This figure shows graphically the changes noted in tracings of Fig. 8. Left to right: *A-C. A*, Daily changes in percentage atrial downstroke (*AD*) amplitude of total complex amplitude (*TA*) over 5 days of digitalization with oral gitalin. A precipitous decrease in this percentage occurred 24 hours after initiation of therapy. An essentially stepwise decrease in this movement occurs with progressive digitalization. *B*, Changes in the percentage of total amplitude occupied by the ventricular ejection downstroke amplitude with progressive digitalization. Unlike the atrial upstroke and downstroke, dramatic response in this parameter did not occur until the fourth day of digitalization (see text for explanation). *C*, The daily effect of digitalis on the percentage atrial downstroke of ejection downstroke amplitude (AD/EDS $\times$ 100). Again, a stepwise decrease occurs with an early marked fall. This relative movement decreased from 288 to 28 per cent. *Record obtained before initiation of digitalis therapy. **Record obtained after full digitalization. *AD:* Atrial downstroke amplitude. *TA:* Total amplitude of complex. *EDS:* Ventricular ejection downstroke amplitude.

The mid-systolic outward movement (Figs. 1 and 8) present in records obtained from patients with untreated biventricular failure resembles that of patients with right ventricular hypertrophy,[14] and is also similar to the bulge seen in patients at the time of anginal pain,[1,2] and in some patients after myocardial infarction.[15] The cause for this is unknown at present.

The mechanisms by which the passive ventricular filling wave increases and the atrial deflections decrease after digitalization are presumably explained as follows. Augmented myocardial contractility is one of the major effects of digitalis.[16-25] This causes more complete emptying, decrease in residual volume,[13,26-30] reduced ventricular diastolic pressure, and usually an increase in stroke volume.[17,26,30] Under these conditions the now less distended ventricle can fill more before pressure equalization with the atrium occurs. Ventricular filling is accomplished to a greater extent by passive rapid filling (Fig. 9) and less by atrial contraction, because the less distended atrium contracts less vigorously.

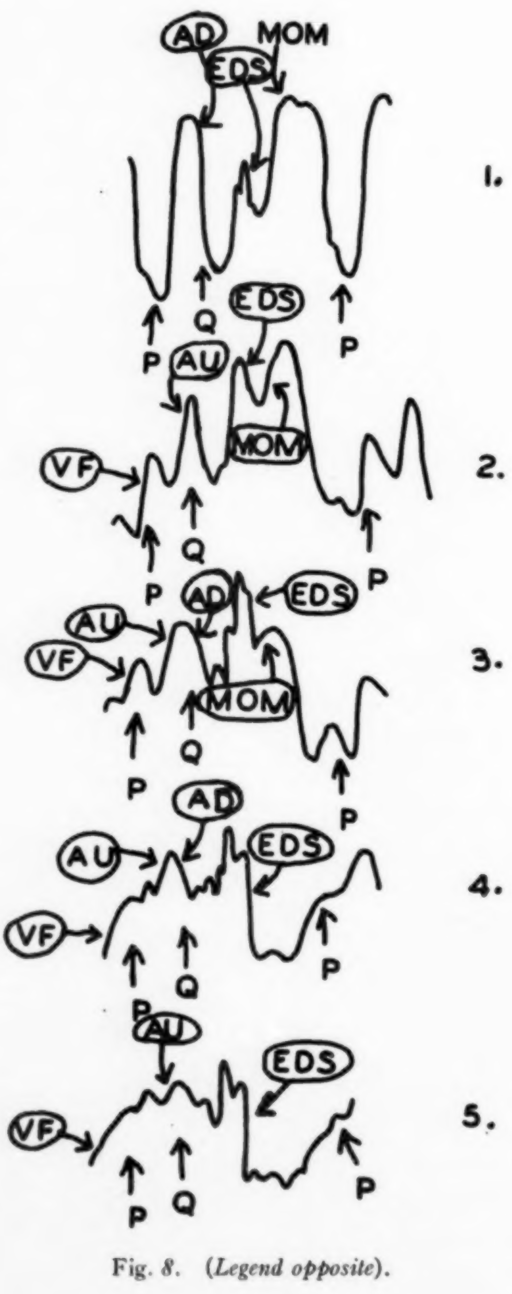

Fig. 8. (*Legend opposite*).

Fig. 8. Shows the daily changes in kinetocardiograms of Patient Q. F., obtained over 5 consecutive days from control to full digitalization, from area K_{24}. *1*, Control record. No digitalis. This record shows the difficulty in interpreting large outward (upward) movements that occur after atrial excitation when not preceded by a definite ventricular filling wave; it is impossible under such circumstances to state how much of this movement is actually due to atrial activity, since both atrial systole and passive ventricular filling may be responsible for its production (see text). The atrial downstroke (*AD*), however, is markedly exaggerated (compare with normal tracing Fig. 1). A small ventricular ejection downstroke (*EDS*) and a large mid-systolic outward movement (*MOM;* bulge) are seen. *2*, Twenty-four hours after initiation of digitalis therapy (3 mg. gitalin), four striking changes have occurred: (a) the appearance of a definite passive ventricular filling wave (*VF*) and atrial upstroke (*AU*); (b) a marked decrease in the atrial downstroke (*AD*); (c) a slight increase in the ventricular ejection downstroke; and (d) a significant reduction in the mid-systolic bulge (*MOM*). *3*, Forty-eight hours after digitalization (5 mg. gitalin) was begun, the same changes as noted in tracing *2* above have occurred, but are slightly greater in degree, the most prominent being the increased *EDS* and decreased *MOM*. *4*, Seventy-two hours after beginning digitalization (7 mg. gitalin), a marked decrease in the atrial movements has occurred with a concomitant increase in the ventricular filling wave (*VF*). The ventricular ejection downstroke now occupies a large percentage of total amplitude and the bulge has essentially disappeared. *5*, At the time of full digitalization (9 mg. gitalin), the most striking changes are a continued increase in the passive ventricular filling movement and continued decrease in the recorded atrial deflections. Note: The heart rate at the time record *5* was taken was the same as that at the time tracing *1* was recorded. *P:* P wave of ECG. *Q:* Q wave of ECG.

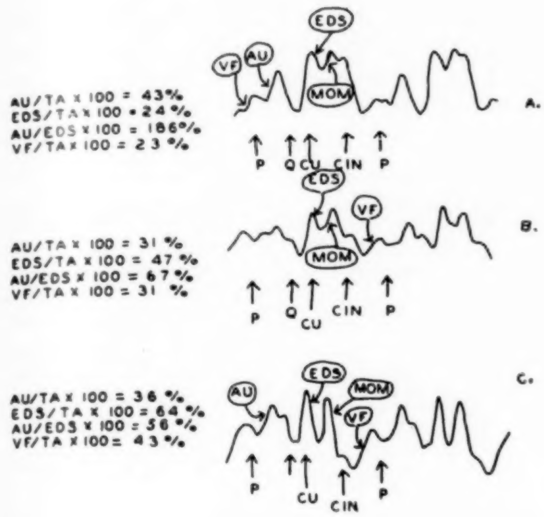

Fig. *9*. This figure illustrates the effect of intravenous lanatoside-C on kinetocardiograms obtained from a patient with marked decompensation (biventricular failure) who had been on maintenance digitalis therapy. All records were taken from K_{24}. *A*, Control record. The atrial upstroke (*A U*) motion is clearly defined as a separate entity, constituting 43 per cent of total amplitude. The ventricular ejection downstroke (*EDS*) is markedly decreased (see normal record Fig. 1), and a prominent, sustained "bulge" (mid-systolic outward movement; *MOM*) is readily visualized. *B*, One hour after 0.2 mg. of lanatoside-C intravenously. The atrial upstroke (*A U*) deflection has become less prominent, the ventricular ejection downstroke (*EDS*) has doubled in amplitude, and the mid-systolic outward movement (bulge; *MOM*) is shorter in duration, being much less sustained than in the control record. The ventricular filling wave has become slightly more prominent. *C*, Two hours after first 0.2-mg. intravenous dose of lanatoside-C, and one hour after second 0.2-mg. intravenous dose. The atrial movement (*A U*) remains below the control values but shows no marked decrease. The ejection downstroke has increased considerably, being approximately three times greater than the control value; similarly, the mid-systolic outward movement is much less sustained. The ventricular filling wave (*VF*) has shown an increase. Note: The patient's heart rate remained at 70 beats per minute throughout the entire procedure, and each record was taken from the same point on the precordium. *P:* P wave of ECG. *Q:* Q wave of ECG. *CU:* Carotid upstroke. *CIN:* Carotid incisural notch.

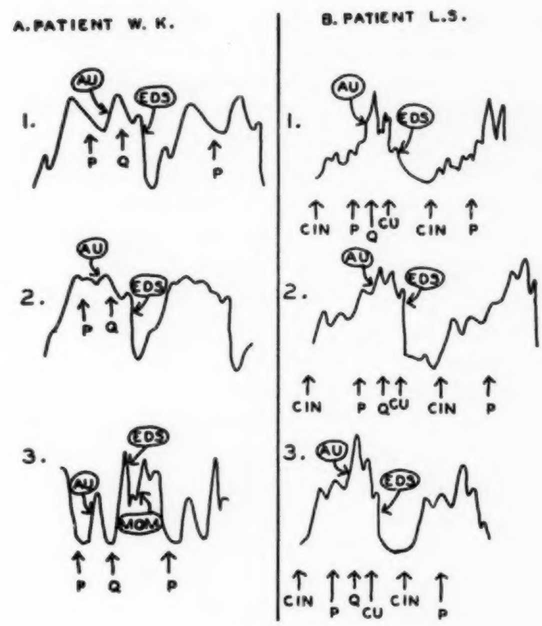

Fig. *10*. This figure shows the kinetocardiographic changes noted at the time of untreated congestive failure, full compensation with therapeutic doses of digitalis, and at the time of digitalis intoxication in two patients, one with moderate and one with severe intoxication. *A*, Records from K_2 area. *1*, Mild, untreated left ventricular failure. Note the prominent but not markedly accentuated atrial upstroke motion (*A U*) and the essentially normal ventricular ejection downstroke (*EDS*) movement. *2*, Full compensation. The atrial upstroke deflection is markedly reduced and the ventricular ejection downstroke remains quite normal. *3*, Severe digitalis intoxication. The atrial movements are now quite conspicuous and accentuated; the ejection downstroke is markedly reduced (compare with *1* above), and a bulge (mid-systolic outward movement; *MOM*) has appeared. KCG criteria (see text) for biventricular failure are met in this record and absent in the first two records, indicating a more severe degree of failure with digitalis intoxication than existed initially. *B*, Records from K_1 area. *1*, Mild, untreated left ventricular failure. A prominent atrial upstroke (*A U*) is present; the ventricular ejection downstroke (*EDS*) is reduced to below 50 per cent of total amplitude. *2*, Full compensation. The atrial upstroke deflection is approximately one half of that seen in the record obtained before therapy was begun, and the ejection downstroke now contributes to 90 per cent of total amplitude. *3*, Moderate digitalis intoxication. The atrial upstroke is now approximately the same as that seen in the initial record (*B,1*); the ventricular ejection downstroke is reduced but does not approach that seen in the control record. Abbreviations: *CU*, Carotid upstroke. *CIN*, Carotid incisural notch. *P*, P wave of ECG. *Q*, Q wave of ECG.

Consequently, a reduction in recorded amplitude of atrial movement occurs.[31] Fig. 7 shows that the decline in atrial motions preceded the increase in the ventricular ejection downstroke. This is interpreted to indicate that a slight reduction in ventricular residual volume and pressure causes a marked decrease in the distention of the thin-walled atrium. Thus, the force of the atrial contraction and atrial deflections, as recorded by the KCG, decreases as improvement occurs. This is in keeping with the work of Stead and associates,[16] who found a fall in atrial pressure to be the first change noted after the intravenous administration of digitalis.

With progressive digitalization, patients with severe cardiac failure of long duration demonstrated slower changes in atrial movements than did those with moderate decompensation. It is likely that digitalis in the former patients was not capable of producing full compensation because of less reversibility of the prolonged untreated state. This is consistent with the findings of Ferrer and associates,[32] who showed that pulmonary arterial pressures fell to normal limits shortly after intravenous digitalis was administered in those patients with mild to moderate failure; longer time was required for this same effect in those more incapacitated.

It has been reported[33-37] that patients develop an increase in the severity of congestive failure with digitalis intoxication. Objective evidence for this is shown through the KCG. The similarity of records obtained from patients at the time of digitalis intoxication and when untreated is marked.

Summary

Kinetocardiographic alterations before and after digitalis therapy in patients with congestive heart failure are presented. The most consistent finding during failure was an increase in the atrial movements, which decreased to normal levels after maximal doses of digitalis. Inconsistent alterations in ventricular ejection movements were noted.

Patients in failure had decreased passive ventricular filling waves, which increased after digitalization. A possible explanation for this is presented.

Digitalis intoxication produced changes in kinetocardiograms that resembled those seen in untreated patients with failure, thus offering objective evidence that an excess of this drug will cause an increase in failure.

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Kinetocardiographic alterations in patients with congestive heart failure at rest and after exercise
The effect of digitalis

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Having previously reported the effects of heart failure on the kinetocardiogram, as determined during the resting state,[1] we now report on the changes produced by physical effort in patients with heart failure as compared to normal subjects. The effectiveness of digitalis in preventing these exercise-induced alterations will also be reported.

Methods

Recordings of low-frequency precordial movements (kinetocardiogram; KCG) were made with the bellows-crossbar technique,[2] using a 6-channel Sanborn direct writer. ECG and carotid pulse curves were simultaneously obtained. All tracings were recorded at the end of a normal expiration and from the fourth intercostal space in the left parasternal line.

After control resting tracings were taken, each patient was exercised from 30 seconds to 2 minutes, depending on the clinical status; 2 minutes of exertion were used for all normal subjects. This physical effort consisted of moving, while the subject was recumbent, a 10-pound pulley-weight system a distance of 8 feet every 3 seconds. Recordings were made at ½, 1, 2, 4, 6, 8, and 10 minutes after completion of the exercise.

Two movements were considered: first, an outward (upward) deflection occurring at the time of atrial systole; second, an inward (downward) motion appearing at the time of rapid ventricular ejection. Both were expressed as a percentage of total amplitude (TA), the latter being determined by measuring the distance from the highest to the lowest point of a complete cardiac cycle complex (Fig. 1).

The measurement of the ejection downstroke (EDS) was readily achieved because, in the precordial area studied, this movement begins 0.12 to 0.16 second after the onset of ventricular excitation and at about the time of the start of the carotid upstroke. The separation of the atrial upstroke (AU) movement from the outward deflection due to passive ventricular filling (VF) presented some difficulty when the rate was rapid. Under these circumstances, filling may start after the onset of the P wave, and the two outward motions may be fused. Consequently, only those complexes were studied which presented two distinct upward

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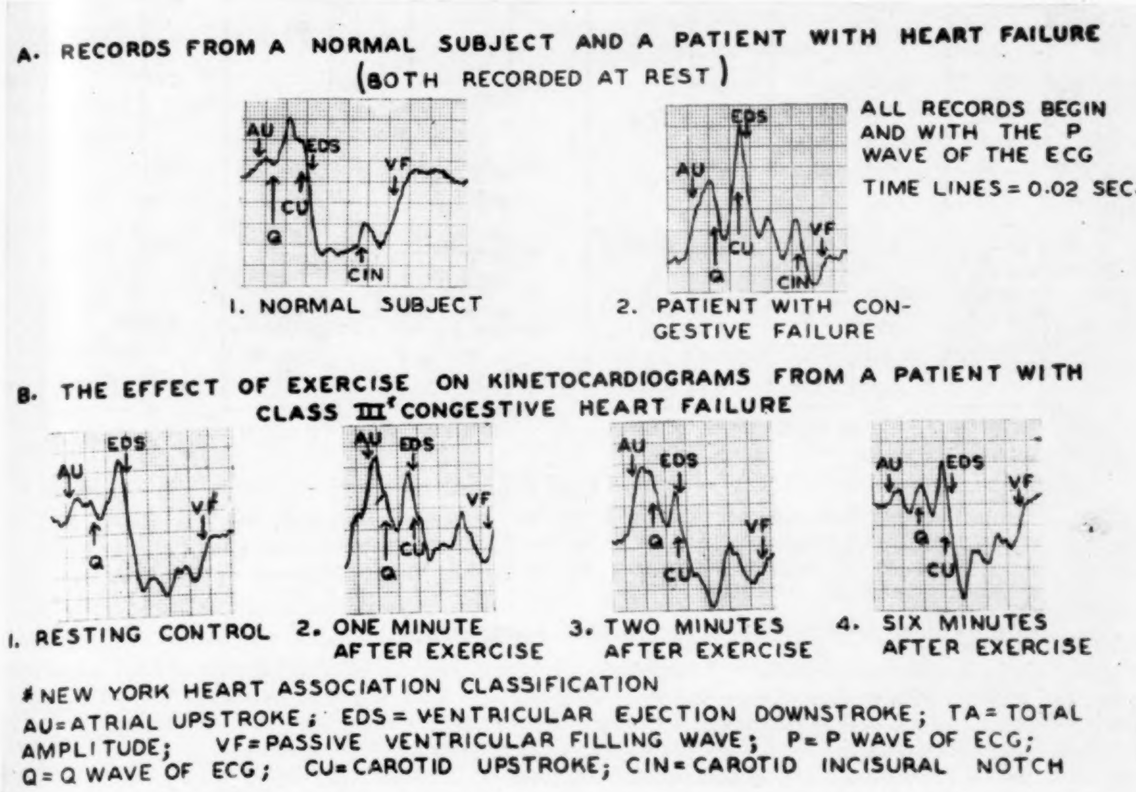

Fig. *1.* This figure shows a comparison of resting records obtained from a normal subject and from a patient with symptomatic congestive heart failure. The effect of minimal exertion on kinetocardiograms from a patient with Class-III failure is shown. (The patient was exercised for one minute while supine by using two 5-pound weights on a pulley-weight system. These were moved a distance of 8 feet every 3 seconds; twenty complete pulls were utilized.) All records begin with the P wave of the ECG to better demonstrate the marked changes which occur in diastole. *A*, Comparison of resting kinetocardiograms. *1*, Note the essentially absent atrial upstroke (*AU*) motion, the large passive ventricular filling wave (*VF*), and the prominent ventricular ejection downstroke (*EDS*). *2*, The passive ventricular filling wave is markedly reduced, the atrial upstroke is quite large, and the ejection downstroke is decreased, in relation to the total amplitude. *B*, Effect of exercise on kinetocardiograms. *1*, This record could be considered normal since all movements studied are within normal limits. *2*, The record now becomes abnormal. The atrial movement has increased, ejection downstroke decreased, and the ventricular filling wave has changed little. *3*, The atrial movement has continued to increase, the ejection downstroke remains decreased, and the ventricular filling wave is markedly reduced. *4*, The record now has again become essentially normal.

deflections with the second (atrial upstroke; AU) starting 0.04 to 0.10 second after the beginning of atrial excitation.

Three percentages were determined: AU/TA × 100, EDS/TA × 100, and AU/EDS × 100. Fig. 1 shows the movements considered in this communication.

Subjects

Normal values were obtained from 15 subjects who were over 35 years of age, none of whom had any evidence of cardiac disease. A total of 28 studies were performed on 22 patients with known heart disease; these were given a classification of their cardiac status according to standards established by the New York Heart Association.[3] Each was independently evaluated by two or more observers before any studies were initiated.

Thus, this report includes studies on 15 normal subjects, 10 on patients with Class-I, 11 on patients with Class-II, 6 on patients with Class-III, and 1 on a patient with Class-IV heart disease. Table I presents the clinical data on the patients. Four were studied before, during, and after digitalization, so that the effects of exercise on kinetocardiograms from the same patient with varying degrees of compensation were recorded. No record was included that was obtained at the time of anginal pain.

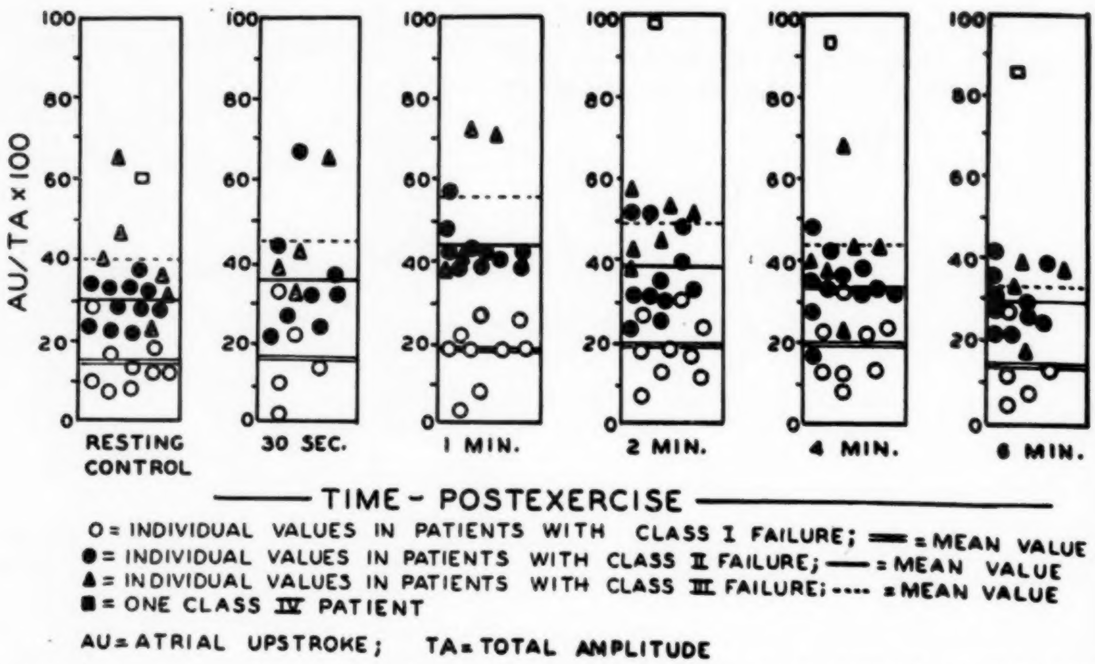

Fig. 2. This figure shows a comparison of the relative atrial upstroke amplitudes (AU/TA × 100) in the three groups of patients with cardiac disease that were studied (New York Heart Association's Class I-III), both during the resting state and 30 seconds to 6 minutes after exertion. *Resting Control:* Overlapping occurs with all three groups. The range for the Class-I patients was 8 to 29 per cent (mean, 15 per cent); Class-II, 23 to 38 per cent (mean, 30 per cent); and Class-III, 23 to 65 per cent (mean, 40 per cent). *30 Seconds Postexercise:* Complete separation of the three groups does not occur, and the means show only a minimal increase over control values. *1 Minute Postexercise:* Class-II and Class-III patients are now completely separated from Class-I patients; the highest value for the Class-I group is 26 per cent, and the lowest for the Class-II and Class-III subjects is 37 per cent. Mean values have shown a corresponding increase. *2 Minutes Postexercise:* Five of the Class-II patients and all Class-III patients are beyond the limits established for normal. All Class-I subjects have continued to stay within the normal range. *4 Minutes Postexercise:* Five each of the Class-II and Class-III patients show values beyond the upper limits of normal; however, the mean value for the former group is now within the normal range. *6 Minutes Postexercise:* Three Class-II and 2 Class-III patients continue to show abnormal values. The mean value for each group is now in the normal range. Thus, no separation of normal subjects and Class-I patients can be made through the use of this criterion. Differentiation of both of these groups from Class-II and Class-III patients is possible when the changes in this motion produced by exercise are evaluated. Note: Because of marked dyspnea, records could not be made from the one Class-IV patient at ½ and 1 minute after exertion.

Since patients with mitral or tricuspid valvular disease may have atrial distention and exaggerated atrial movements even in the absence of failure, such individuals were not studied.

Results

Each of the relative movements studied will be considered separately.

Atrial upstroke motion. The normal subjects and the group of patients with asymptomatic heart disease (Class I) showed no relative atrial outward movements greater than 30 per cent at rest or 33 per cent after exercise (Table II). Forty-six per cent of the Class-II and 83 per cent of the Class-III patients had values in excess of 30 per cent at rest; after exercise, all had such relative motions greater than 33 per cent. Serial postexertional recordings (Fig. 2) showed that the greatest atrial upstroke–total amplitude ratio occurred 1 minute after cessation of physical effort. Return to the resting control level varied from 2 to 8 minutes; 2 patients, one each in the Class-III and Class-IV groups, failed to reach their initial levels 10 minutes after exertion. Fig. 3,*A* compares the changes in wedge pressure produced by exercise in normal subjects and in patients with failure. Fig. 3,*B* shows a comparison of resting and postexertional atrial movements from normal subjects and from patients of each failure group studied. The Class-II and Class-III patients had resting percentages that were interspersed with normal ones; however,

complete separation of these latter two groups from the normal subjects and Class-I patients could be made on the basis of this movement 1 minute after physical effort. Separation of Class-II from Class-III patients is not possible through the use of this criterion, except perhaps in those with values in excess of 60 per cent. However, by means of the changes produced in this relative motion by exertion, separation of the patients of Class I from those of Class II and Class III was possible.

Ventricular ejection downstroke movement. The resting mean value for this motion in normal subjects was 62 per cent at rest and 55 per cent at 1 minute postexercise. This pattern of essentially no change from control percentages after physical effort was seen in each group studied. However, it is obvious (Fig. 4) that this relative motion decreases markedly with each successive increase in the severity of failure, even though no consistent difference exists between the resting and postexertional state.

Atrial upstroke–ventricular ejection downstroke ratio (*AU/EDS*$\times$*100*). Table II shows ranges and means for this parameter before and after exercise in the normal subjects and in patients with Class-I to Class-III heart disease. An arbitrary value of 0 to 50 per cent was established as physiologic. On the basis of this criterion, 7 per cent of normal subjects, 50 per cent of Class-I, 91 per cent of Class-II, and 100 per cent of Class-III patients had values in excess of 50 per cent after exercise. Thus, this parameter proved to be the only one used that allowed even a beginning separation of normal from Class-I subjects.

Effect of digitalis on kinetocardiograms. Table III shows a varying amount of decrease in the AU/TA ratios after the administration of digitalis to the 4 patients studied in this manner. Fig. 5 shows results

Table I. *Clinical data on patients studied*

Name	*Age (yr.)*	*Sex*	*Diagnosis*	*Therapy*	*Classification*†	*Vital capacity (% normal)*
J. J.	56	M	CAD	Digitalis	I	—
M. R.*	69	M	CAD	Digitalis	I	73
J. W.*	59	M	AI	Digitalis	I	74
L. P.	15	F	EC	None	I	—
N. W.	66	M	CAD	None	I	79
E. M.	51	M	AI	Digitalis	I	—
L. H.	43	F	HHD	None	I	84
J. W.	15	M	ASD	None	I	—
C. H.	12	M	ASD	None	I	93
O. W.	50	M	AS	None	I	—
W. K.*	52	M	AI	Digitalis	II	56
M. D.*	60	F	CAD	None	II	75
M. S.	44	F	Myocarditis	Digitalis	II	68
M. N.	70	F	CAD	Digitalis	II	75
M. R.*	69	M	CAD	Digitalis	II	68
M. D.*	60	F	CAD	Digitalis	II	75
J. W.*	59	M	AI	Digitalis	II	65
J. M.*	26	M	AI	Digitalis	II	70
A. C.	45	M	Pericarditis	Digitalis	II	70
H. A.	59	M	HHD	Digitalis	II	83
D. C.	57	M	AI	Digitalis	II	86
W. K.*	52	M	AI	Digitalis	III	56
J. F.	61	M	CAD	Digitalis	III	85
H. W.	55	M	CAD	Digitalis	III	—
F. O.	63	M	CAD	Digitalis	III	88
J. W.*	59	M	AI	Digitalis	III	46
J. M.*	26	M	AI	Digitalis	III	61
J. J.	46	M	Myocarditis	Digitalis	IV	—

*Studies done at more than one level of classification.
†Classification according to New York Heart Association.
CAD: Coronary artery disease AI: Aortic insufficiency. EC: Eisenmenger's complex. HHD: Hypertensive heart disease. ASD; Atrial septal defect. AS: Aortic stenosis,

Table II. *Range and means for each parameter studied in normal subjects and patients with Class I-III heart disease**

Parameter			Normal (15 subjects)	Class I (10 patients)	Class II (11 patients)	Class III (6 patients)
AU/TA × 100	Resting control	Range	0–27%	8–29%	23–38%	23–65%
		Mean	12%	15%	30%	40%
		Comment	None > 30%	None > 30%	5 > 30%	5 > 30%
	1 min. post-exercise	Range	0–33%	7–26%	37–57%	38–72%
		Mean	16%	19%	43%	55%
		Comment	None > 33%	None > 33%	All > 33%	All > 33%
EDS/TA × 100	Resting control	Range	24–96%	17–80%	5–67%	0–65%
		Mean	62%	49%	38%	26%
		Comment	3 < 50%	4 < 50%	8 < 50%	4 < 50%
	1 min. post-exercise	Range	21–92%	6–74%	2–91%	0–45%
		Mean	55%	39%	39%	23%
		Comment	6 < 50%	5 < 50%	9 < 50%	All < 50%
AU/EDS × 100	Resting control	Range	0–83%	10–71%	28–1,000+%	35–1,000+%
		Mean	21%	33%	204%	154%
		Comment	1 > 50%	2 > 50%	9 > 50%	5 > 50%
	1 min. post-exercise	Range	0–155%	10–120%	37–1,000+%	160–1,000+%
		Mean	30%	59%	192%	239%
		Comment	1 > 50%	5 > 50%	10 > 50%	All > 50%

*New York Heart Association classification.
AU: Atrial upstroke. EDS: Ventricular ejection downstroke. TA: Total amplitude.

Table III. *Relative atrial upstroke amplitudes* ($AU/TA \times 100$) *at rest and after exercise before and after digitalization*

Patient	Control		1 min. postexercise		2 min. postexercise		4 min. postexercise		8 min. postexercise		Vital capacity (% normal)		Total amount of digitalis (gitalin)
	BD	AD	BD	AD	BD	AD	BD	AD	BD	AD	BD	AD	
J. W.	65	13	70	25	58	19	69	9	70	9	46	74	11.0 mg.
W. K.	30	24	—	57	52	52	40	27	37	32	56	56	5.0 mg.
M. R.	23	19	39	19	31	24	33	24	22	22	68	73	7.0 mg.
J. M.	40	34	—	43	45	35	44	35	46	35	61	70	7.0 mg.
Mean	39.5	22.5	55	22	46	32	46	24	44	25	58	68	

BD and AD: Before and after digitalization, respectively. AU: Atrial upstroke. TA: Total amplitude.

obtained from one patient at different levels of compensation after various amounts of the drug. This patient, who, after digitalization exhibited the most striking rise in vital capacity, also showed a marked decrease in relative atrial motions. The 3 patients who displayed little or no rise in vital capacity showed less impressive evidence of improvement in this KCG deflection.

Discussion

This study has revealed that a marked exaggeration in kinetocardiographic atrial movements occurs after minimal effort in those patients with Class-II and Class-III heart disease. Resting values for this motion were normal in some of the Class-II and Class-III patients, whereas *all* demonstrated exaggerated atrial deflections after exercise. The ventricular ejection down-

stroke was noted to be decreased in these same patients while at rest, with no consistent further decrease after effort. No marked change occurred in normal and Class-I subjects. Thus, confirmation is offered for earlier observations[4] on kinetocardiograms obtained from patients with heart failure.

Previous work done in this laboratory[1] attributed the increased relative atrial movements that occur in patients with failure to atrial distention resulting from an increase in ventricular diastolic pressure. This produces an increased vigor of atrial contraction and, thus, an increased amplitude of recorded atrial movements. Similarly, the decrease in ventricular ejection downstroke was attributed to decreased contractility, cardiac output, and change of volume as ventricular ejection occurs.

An explanation for the increase in atrial movements which occurs and persists *after* exertion could possibly reside in a relationship to venous pressure. This, in turn, appears to be related to changes in oxygen supply and peripheral anaerobic metabolism. Therefore, changes in venous pressure and in tissue metabolism which are known to occur in heart failure will be briefly presented.

That the degree of rise of peripheral venous pressure after exercise is well correlated with the severity of failure has been shown.[5-7] Richards[8] found that, in contradistinction to normal subjects, patients with failure have essentially no gradient between peripheral and central venous pressures. Atrial pressure in man has been shown to increase with failure, irrespective of change in cardiac output,[9-14] and many with normal resting pressures develop abnormal values after exertion. This phenomenon has also been observed in the experimental animal.[15] Not only does venous pressure increase, it remains elevated for a longer period of time. Our study showed that the greater the degree of failure, the longer were the atrial movements exaggerated. Thus, the duration of elevation of these deflections apparently reflects the

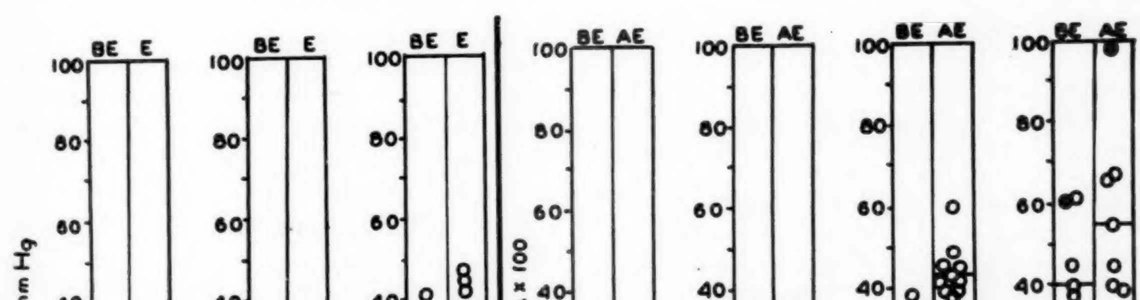

Fig. 3. *A*, The effect of exercise on the pulmonary capillary (wedge) pressure in normal subjects and in patients with congestive heart failure (data of Dexter, et al.[14] and Lewis, et al.[13]). Note that 4 of 5 patients with normal wedge pressures at rest developed an increase in this measurement with exercise. All but one patient of the group with an abnormal wedge pressure at rest had an increase in atrial pressure with exercise. *B*, Postexercise ratio of atrial upstroke movements to total amplitude (AU/TA × 100) in normal subjects and in patients with Class I-IV congestive heart failure (New York Heart Association classification). Note that no essential difference exists between the normal subjects and Class-I patients. Forty-six per cent of Class-II and 83 per cent of the Class-III patients had abnormal resting values; after exercise, all had atrial movements which exceeded normal limits.

status of the ventricular reserve capacity, i.e., the rapidity of recovery after exertion. Fig. 5 demonstrates this. In this patient the administration of digitalis first resulted in normal resting atrial movements. Post-exertional values were abnormal, but for only 5 minutes of the 10-minute study period; before digitalis was given, these values were exaggerated during the entire study period. Larger amounts of the drug resulted in normal values, both before and after exercise.

Ford and associates[16] demonstrated that the greater cost of exercise is deferred to the recovery period in patients with cardiac disease. Thus, the increased atrial movements seen in this study appear to be the result of *an inability of the ventricles to meet the inflow load during the recovery phase of exercise.* It is known that higher levels of blood lactic acid have been found in patients with failure than in normal subjects,[17-22] and this difference increases with

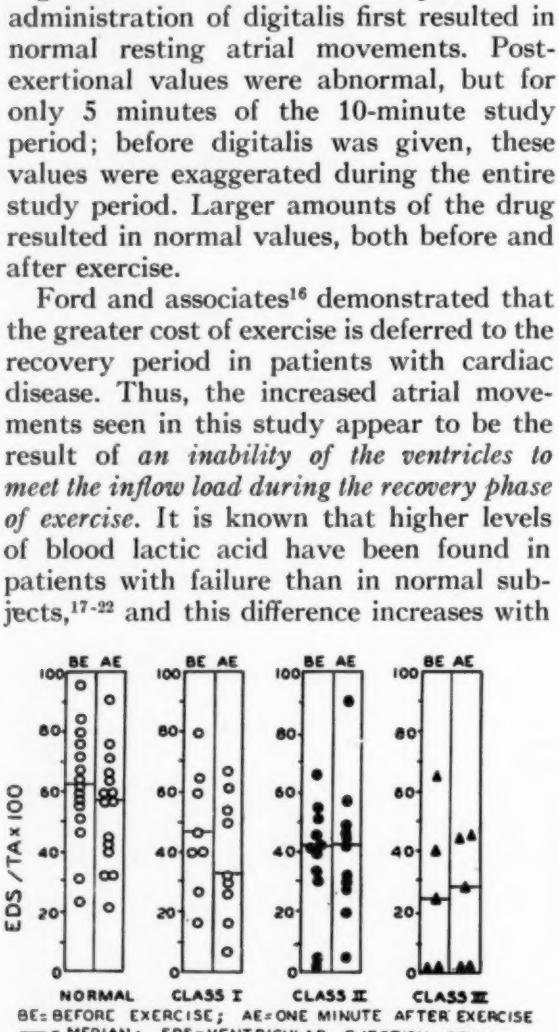

Fig. *4*. This figure compares the pre- and postexertional ventricular ejection downstroke values (EDS/TA × 100) in the four groups studied (normal subjects to Class-III cardiac patients). *Normal.* This value ranged from 24 to 96 per cent before exercise and from 21 to 92 per cent at 1 minute after exercise. Three values at rest and six after exertion were below 50 per cent. *Class I.* The resting range was 17 to 80 per cent, with five values below 50 per cent. After exercise, this range was 6 to 67 per cent, with five below 50 per cent. *Class II.* Ranges were 5 to 67 per cent and 2 to 91 per cent at rest and after exertion, respectively. Three values at rest and two after exercise were *above* 50 per cent. *Class III.* Only one value at rest and none after exercise were *above* 50 per cent. Little change occurred in the post-exertional state when compared with the resting state; however, median values showed a progressive decrease from the normal to the Class-III group. (Classification of heart failure according to the New York Heart Association.)

exertion. A delayed return of the level of blood lactate to resting values was noted. Regan and associates[23] found a reduction in arterial-venous lactate difference within 15 minutes after the administration of acetyl strophanthidin to patients with heart failure.

Huckabee and associates[17,18] found that patients with Class-I heart disease had adequate oxygen transport with mild exercise, and that the rate of lactate accumulation or rate of anaerobic metabolism was no different from that of normal subjects. In this type of patient, the body tissues had to rely on anaerobic metabolism to only a small extent. In patients with definite failure (Class II or greater), oxygen transport was only 50 to 80 per cent effective in meeting body requirements, and a further increase in cardiac output of 40 to 90 per cent would have been necessary to effect such. It was the conclusion of these authors that during exercise most patients with failure have an inadequacy of oxygen supply rates to satisfy tissue energy requirements, and this, in turn, was due to an insufficient cardiac response. Our studies showed that normal subjects and Class-I patients had very similar responses as regard atrial motions, whereas the reverse was true when an impairment of Class II or greater existed. On the basis of Huckabee's work, the duration of elevation of these movements may perhaps be interpreted as a reflection of the ability of the ventricles to empty themselves and thereby to supply tissue oxygen; i.e., the longer the elevation, the higher the ventricular diastolic pressure and the worse the failure.

The dramatic reversal of abnormal motions which may occur after digitalis (Fig. 5) can be attributed to the increase in myocardial contractility effected by this drug.[24] Thus, ventricular emptying is enhanced, and residual volume is decreased, as is ventricular diastolic pressure; the resultant is a decrease in atrial distention and pressure. The ventricle can now meet the inflow load presented it during the postexercise period.

The changes in precordial motions produced by exercise appear to be related to heart failure and not to heart disease. This would offer an explanation for the absence of changes in Class-I patients and the

DESIGNATION	WEIGHT	VITAL CAPACITY	CIRCULATION TIME **	CLASSIFICATION *	GITALIN #
A	171	2.0 l.	28 SEC.	III	0 MG.
B	168	2.8 l.	----------	II	7 MG.
C	163	3.2 l.	23 SEC.	I	11 MG.

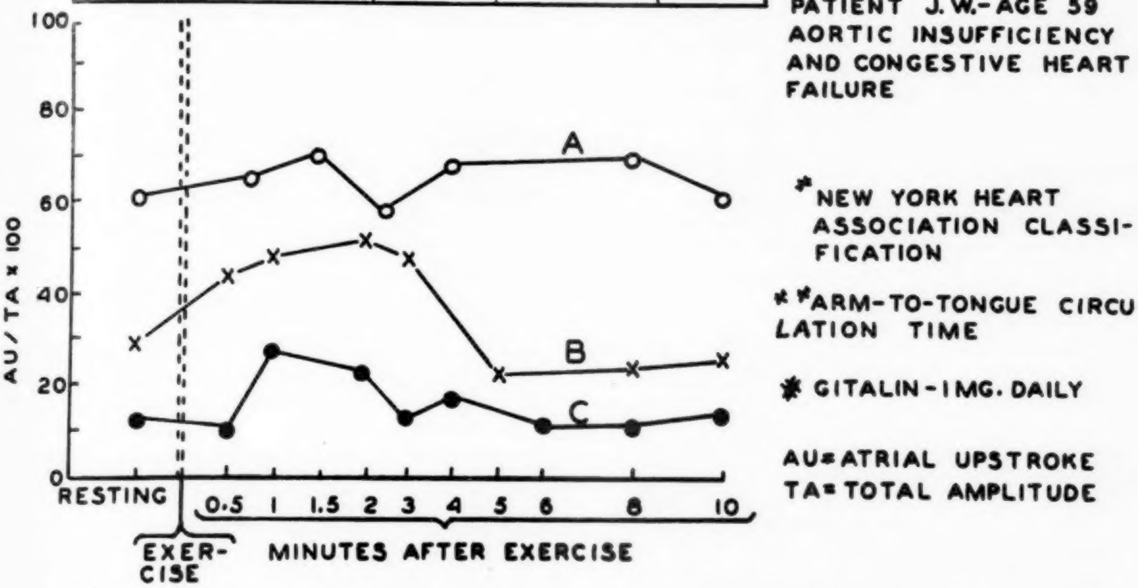

Fig. 5. Relative atrial upstroke amplitudes (AU/TA × 100) in one patient, at the same level of exercise, before, during, and after digitalization. The patient was admitted to this study at a time when he was receiving a small daily dose of digitalis but was, for all practical purposes, totally undigitalized. *A*, Initial study. The values are all grossly abnormal. Clinically, the patient was considered to be in Class III; vital capacity was reduced and circulation time prolonged. *B*, After 7.0 mg. of oral gitalin. Vital capacity showed an increase, weight decreased 3 pounds, and, clinically, the patient was less incapacitated. Atrial movements at rest were within normal limits, but after exercise they were definitely abnormal for 5 minutes of the 10-minute study. *C*, After 11.0 mg. of oral gitalin. Control and postexertional relative atrial movements were all within the range established for normal. A total increase in vital capacity of 1.2 liters, a decrease in arm-to-tongue circulation time of 5 seconds, and a decrease in weight of 8 pounds occurred.

presence of such alterations in the more advanced classes. Thus, small amounts of effort in patients with symptomatic decompensation are readily reflected by an exaggeration of relative atrial deflections; these, in turn, reflect atrial pressure and distention. In addition, the effect of digitalis can be at least partially observed through the use of this method.

Summary

1. Twenty-eight studies were done on 22 patients with cardiac disease who varied from asymptomatic (Class I) to definitely decompensated (Class II or greater). The results were compared with those in 15 normal individuals.

2. Class-I patients had normal resting and postexertional relative atrial movements. Forty-six per cent of Class-II and 83 per cent of Class-III patients had abnormal atrial movements at rest; after exercise, all showed values in excess of those established for normal. An explanation is postulated for this finding.

3. Four patients were given varying amounts of digitalis, after which studies were made during the resting and postexertional state. All showed a reduction of the exaggerated atrial movements; in 1, a marked change occurred; in 2, a moderate change; and in 1, only a slight decrease was noted. In each, however, a tendency toward an increased tolerance to exercise was noted.

4. Changes in precordial movements as determined by this method are in remarkable agreement with those determined by the more complex procedure of cardiac catheterization with measurement of wedge and other pressures.

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The electrocardiogram of the premature infant

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The electrocardiograms of normal full-term infants and of children[1-7,17] have been thoroughly studied and reported upon, but few studies have been done on the premature infant. It is the purpose of this paper to report the results of a study of the electrocardiograms of premature infants who have survived, as part of a larger study of the cardiopulmonary status of the premature infant.

Methods and Materials

All of the patients studied were born prematurely at the Philadelphia General Hospital, or brought to the nursery for premature infants shortly after their birth. Of the 143 patients studied, approximately 97 per cent were non-white. The electrocardiograms were taken as soon as possible on the first day of life, and repeated when the infants were 6 weeks old, and again when they were 3 months old. The body temperature of the infants on their first day of life had stabilized above 37° C. A complete physical examination was performed on every patient on the same day that the electrocardiogram was taken. A number of chest x-ray films were made; in no instance was physical or roentgenographic evidence of cardiac disease detected. In all cases the electrocardiograms were taken on nonsedated babies. On occasion, a bottle of glucose water or formula was used to pacify these infants.

The electrocardiographic machine used was a direct-writing Sanborn Model No. 51. The limb electrodes were the standard infant size. The exploring chest lead was modified according to the size of the infant. In the smaller babies the precordial electrocardiogram was taken with the tip of the electrode, whereas a Welsh Self-Retaining Infant ECG electrode was used on the larger infants. Sterile electrocardiographic paste or an alcohol sponge was used on the skin. The leads of the electrocardiograms taken were the Standard Limb Leads I, II, III; aV_R, aV_L, aV_F; and V_1, V_2, V_3, V_4, V_5, V_6, and V_{4R}. In the smaller premature infants, Lead V_3 was omitted. The axis was determined by a modification of the Bayley triaxial reference system.[16]

Results

A total of 143 patients was studied. In all, 249 electrocardiograms were obtained. The patients were divided into three groups according to their weight at birth. This was done in order to separate the smaller infants with a higher mortality rate from the larger infants with a lower mortality rate,[15] and to determine whether a difference due

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Table I. *Number of ECGs taken at each age in each of the three groups*

	A (*1 day old*)	*B* (*6 wk. old*)	*C* (*3 mo. old*)
Group I (800-1,300 grams)	16	12	5
Group II (1,300-1,800 grams)	36	20	9
Group III (1,800-2,300 grams)	91	48	13

Table II. *Mean heart rate* ± *standard deviation* (*beats per minute*)

	A	*B*	*C*
Group I	140 (± 11)	180 (± 16)	174 (± 18)
Group II	140 (± 11)	177 (± 8)	180 (± 11)
Group III	135 (± 28)	166 (± 17)	177 (± 24)

Table III. *P-R interval* (*seconds*) ± *standard deviation*

	A	*B*	*C*
Group I	0.11 ± 0.01	0.11 ± 0.02	0.11 ± 0.01
Group II	0.11 ± 0.01	0.11 ± 0.01	0.11 ± 0.01
Group III	0.11 ± 0.02	0.11 ± 0.01	0.12 ± 0.01

to maturation was registered in the electrocardiogram as the infants grew older. The first group consisted of 16 infants who weighed between 800 and 1,300 grams. In this group, 70 per cent were females and 30 were males; 92 per cent were non-white. Twelve of these infants had two electrocardiograms taken at 1 day of age and again at 6 weeks of age; 5 patients of this group also had a third electrocardiogram taken at 3 months of age. The second group consisted of 36 infants who weighed between 1,300 and 1,800 grams. In this group, 50 per cent of the patients were males and 50 per cent were females; 98 per cent were non-white. Twenty of this group of patients had two electrocardiograms taken at 1 day of age and at 6 weeks of age, and 9 of these infants had a third electrocardiogram taken at 3 months of age. The third group consisted of 91 infants who weighed between 1,800 and 2,300 grams. In this group, 40 per cent were males and 60 per cent were females; 98 per cent were non-white. Forty-eight of these infants had two electrocardiograms taken on the first day of life and again at 6 weeks of age, and 13 of these had a third electrocardiogram taken at 3 months of age. (See Table I.)

The following parameters have been studied: The heart rate, the P-R interval, the Q-T interval, the corrected Q-T interval (Q-T_c), and the Q-T ratio $\frac{\text{Q-T}}{\text{Q-T}_c}$, the QRS duration, usually measured in Lead V_1, the axis of the P wave in the frontal plane ($\hat{A}$P), the axis of the QRS complex in the frontal plane ($\hat{A}$QRS), the height of the R wave, in millivolts, in Leads V_{4R}, V_1, and V_6, the ratio of the height of the R wave to that of the S wave in Leads V_{4R} and V_1 (R/S_{V4R}; + R/S_{V1}), and the greatest total voltage, in millivolts, of the R wave plus the S wave measured in Lead V_2 to Lead V_4.

The letters A, B, and C were used to designate the age of the infant. A signified the first day of life; B indicated 6 weeks of age; and C was used for 3 months of age. Representative electrocardiograms from the three groups of patients are shown in Figs. 1-3.

Rate (*Table II*) *and rhythm.* All of the infants in this study had sinus rhythm. One patient had multiple arrhythmias which reverted to a sinus arrhythmia when she was 3 months old. It was not possible to completely rule out heart disease in this baby and for that reason the patient was not included in this report. The mean heart rate on the first day of life was 140 (± 11) beats per minute in Group IA and Group IIA (infants who weighed from 800 to 1,800 grams). In Group IIIA (infants who weighed from 1,800 to 2,300 grams) the mean heart rate on the first day of life was 135 (± 28) per minute. This was a greater range than for the smaller premature babies. There was no significant difference in heart rate for the infants in Groups IB, IIB, and IIIB at 6 weeks of age nor in Groups IC, IIC, and IIIC at 3 months of age.

P-R interval (*Table III*) *and axis of the P wave in the frontal plane* (*Table IX*). The mean value of the P-R interval was 0.11 second in all age groups and at all weights except for the largest premature babies at 3 months of age, Group IIIC. The latter

Table IV. *Mean Q-T interval (seconds)* ± *standard deviation*

	A	*B*	*C*
Group I	0.28 ± 0.05	0.23 ± 0.01	0.26 ± 0.02
Group II	0.28 ± 0.05	0.22 ± 0.03	0.23 ± 0.02
Group III	0.30 ± 0.03	0.24 ± 0.02	0.24 ± 0.02

Table V. *Mean* $Q\text{-}T_c$ *(seconds)* ± *standard deviation*

	A	*B*	*C*
Group I	0.44 ± 0.03	0.39 ± 0.02	0.43 ± 0.01
Group II	0.42 ± 0.02	0.38 ± 0.02	0.40 ± 0.02
Group III	0.44 ± 0.07	0.40 ± 0.01	0.40 ± 0.02

Table VI. *Mean Q-T ratio* $\left(\frac{Q\text{-}T}{Q\text{-}T_c}\right)$ ± *standard deviation*

	A	*B*	*C*
Group I	1.09 ± 0.17	0.99 ± 0.03	1.07 ± 0.02
Group II	1.06 ± 0.02	0.96 ± 0.07	1.00 ± 0.08
Group III	1.09 ± 0.09	1.00 ± 0.08	1.00 ± 0.05

Table VII. *Mean duration of QRS measured in Lead* V_1 *(seconds)* ± *standard deviation*

	A	*B*	*C*
Group I	0.036 ± 0.008	0.038 ± 0.004	0.040 ± 0.001
Group II	0.036 ± 0.007	0.037 ± 0.010	0.039 ± 0.006
Group III	0.037 ± 0.007	0.036 ± 0.007	0.038 ± 0.007

Table VIII. *Mean ÂQRS (measured in degrees)* ± *standard deviation*

	A	*B*	*C*
Group I	103 ± 22	84 ± 34	63 ± 12
Group II	124 ± 20	85 ± 28	82 ± 28
Group III	122 ± 29	85 ± 19	70 ± 19

group of patients had a mean P-R interval of 0.12 second, which closely approximated full-term infants of similar age.[6] There was no evidence of first-degree atrioventricular block in any of the premature infants studied. The P wave in the limb leads of the electrocardiogram on the first day of life usually was of higher amplitude and was peaked in the smaller premature infants. The mean axis of the P wave in the frontal plane was constant, and varied only slightly in all age and weight groups. Usually, it was 60 degrees.

Q-T interval (Table IV), Q-T interval corrected ($Q\text{-}T_c$) *(Table V), and Q-T ratio (Table VI).* The mean value of the Q-T interval was prolonged on the first day of life. The mean value of the $Q\text{-}T_c$ (corrected Q-T interval) on the first day of life was 0.44 second in Groups IA and IIIA, and 0.42 second in Group IIA. The Q-T ratio, $\frac{Q\text{-}T}{Q\text{-}T_c}$, more accurately reflected prolongation of Q-T. The mean value of the Q-T ratio was 1.09 in Group IA, 1.06 in Group IB, and 1.09 in Group IC, whereas in 6-week-old infants the mean Q-T ratio was 0.99 in Group IIA, 0.96 in IIB, and 1.00 in Group IIIA. The mean Q-T ratio in 3-month-old infants was 1.00 in Groups IIIB and IIIC. The mean Q-T ratio in Group IIIC was 1.07 and may not have reflected the true value since only 5 patients were studied.

Duration of the QRS complex, usually measured in Lead V_1 *(Table VII), and axis of the QRS complex in the frontal plane (ÂQRS) (Table VIII).* The duration of the

Table IX. *Mean axis of P wave (measured in degrees)* ± *standard deviation*

	A	*B*	*C*
Group I	60 (± 2)	60 (± 2)	59 (± 1)
Group II	60 (± 2)	59 (± 2)	60 (± 1)
Group III	61 (± 2)	60 (± 2)	60 (± 1)

Table X. *Mean R/S ratio in Lead* V_{4R} ± *standard deviation*

	A	*B*	*C*
Group I	3.5 ± 2.0	3.2 ± 2.8	2.1 ± 2.0
Group II	2.4 ± 1.9	3.1 ± 2.0	2.3 ± 1.6
Group III	2.8 ± 2.7	3.9 ± 3.5	2.2 ± 1.5

Table XI. *Mean R/S ratio in Lead* V_1 ± *standard deviation*

	A	*B*	*C*
Group I	1.5 ± 1.3	2.4 ± 2.0	2.7 ± 0.8
Group II	1.4 ± 1.2	1.6 ± 1.0	1.5 ± 1.0
Group III	1.9 ± 1.9	2.3 ± 1.4	1.3 ± 0.9

Table XII. *Mean height of R wave in Leads V_{4R}, V_1, and V_6 (in millivolts) ± standard deviation*

	A			B			C		
	V_{4R}	V_1	V_6	V_{4R}	V_1	V_6	V_{4R}	V_1	V_6
Group I	5 (±3)	8 (±2)	5 (±3)	10 (±6)	9 (±4)	10 (±6)	7 (±2)	14 (±4)	15 (±3)
Group II	7 (±1)	7 (±4)	7 (±3)	7 (±3)	10 (±3)	1 (±6)	7 (±4)	10 (±5)	12 (±7)
Group III	7 (±3)	9 (±2)	6 (±4)	6 (±2)	9 (±2)	10 (±6)	7 (±2)	10 (±3)	14 (±5)

QRS complex as usually measured in Lead V_1 had a consistent set of values on the first day of life. The minimum value was 0.02 second in Groups IA and IIA, and 0.30 second in Group IIIA. The maximum value in Group IIIA was 0.06 second, and there was no other measurement that exceeded this. The mean values for all groups at all ages was fairly constant.

The axis of the QRS complex in the frontal plane (ÂQRS) followed a similar pattern. On the first day of life the mean values were 103 (± 22 degrees) in Group IA, 124 (± 20 degrees) in Group IIA, and 122 (± 29 degrees) in Group IIIA. There was a shift in ÂQRS to the left at 6 weeks of age, as shown in the tracings, and a smaller shift to the left as demonstrated by the mean values of ÂQRS at 3 months of age.

Ratio of R/S in Leads V_{4R} and V_1 (Tables X and XI), height of R wave in Leads V_{4R}, V_1, and V_6 (Table XII), greatest total voltage of the R+S waves measured in Leads V_2 to V_4 (Table XIII). There was a slight decline in the R/S ratio in Lead V_{4R} as the infant grew from the time of birth to 3 months of age. The height of the R wave in Lead V_{4R} did not change significantly from birth to 3 months of age; therefore, the decline in this ratio was due to an increase in the S wave in the electrocardiogram of these patients at 3 months of age.

Table XIII. *Mean ± standard deviation. Greatest total voltage of R+S measured in Lead V_2 to V_4*

	A	B	C
Group I	23 ± 9	28 ± 4	33 ± 7
Group II	26 ± 9	27 ± 6	31 ± 6
Group III	27 ± 7	28 ± 9	31 ± 6

At birth, the R waves in Leads V_{4R} and in Lead V_6 were of comparable height. There was a somewhat taller R wave in Lead V_1 than in Leads V_{4R} and V_6. The R wave in Lead V_6 of the electrocardiogram increased slightly in height in all groups as the infant grew from birth to 3 months of age.

In the first 24 hours of life many premature infants had an R/S ratio in the right precordial leads of less than 1.0. This indicated that the S wave was of greater amplitude than the R wave. This pattern was present in 25 per cent of the infants in Group IA, in 36 per cent of the infants in Group IIA, and in 39 per cent of the infants in Group IIIA. As the infant matured from 6 weeks to 3 months of age, the pattern changed and the R wave in the right precordial leads became equal to or larger than the S wave.

The mean value of the greatest total voltage of the R+S waves measured in Lead V_2 to Lead V_4 varied only slightly in all of the infants studied. It was well below the value of 50, which is given as top normal in full-term infants and in children.[19]

T wave and RS-T segment. In a great majority of the electrocardiograms of all the premature infants the T waves were inverted in the right precordial leads and upright in the left precordial leads. There were no patients in Group IA (infants who weighed from 800 to 1,300 grams) who had upright T waves on the first day of life. Three per cent of the infants in Group IIA and 13 per cent of those in Group IIIA had upright T waves in the right as well as in the left precordial leads at birth. When the infants were 6 weeks of age, all of the electrocardiograms showed inverted T waves in the right precordial leads.

The RS-T segment was isoelectric in nearly all of the electrocardiograms taken.

Discussion

The typical electrocardiogram of the premature infant showed sinus rhythm at a mean heart rate of 135 (± 28). There was no great difference in heart rate due to the weight of the baby at birth. Ziegler[1] gave a heart rate of 115 to 130 in full-term infants, on the first day of life. Vanoni's series of premature infants[12] had a mean heart rate of 135 per minute on the first day of life. The mean heart rate increased at 6 weeks of age but remained at that level at 3 months of age. There was no significant difference in heart rate among the three groups at the various birth weights, at 6 weeks of age and at 3 months of age. All of the infants at 6 weeks of age and at 3 months of age had sinus rhythm, and no arrhythmias were encountered.

The mean P-R interval was 0.11 second in all groups except Group IIIC. This group had a P-R interval of 0.12 second. This agreed with the results in earlier studies[5,6] in full-term infants. However,

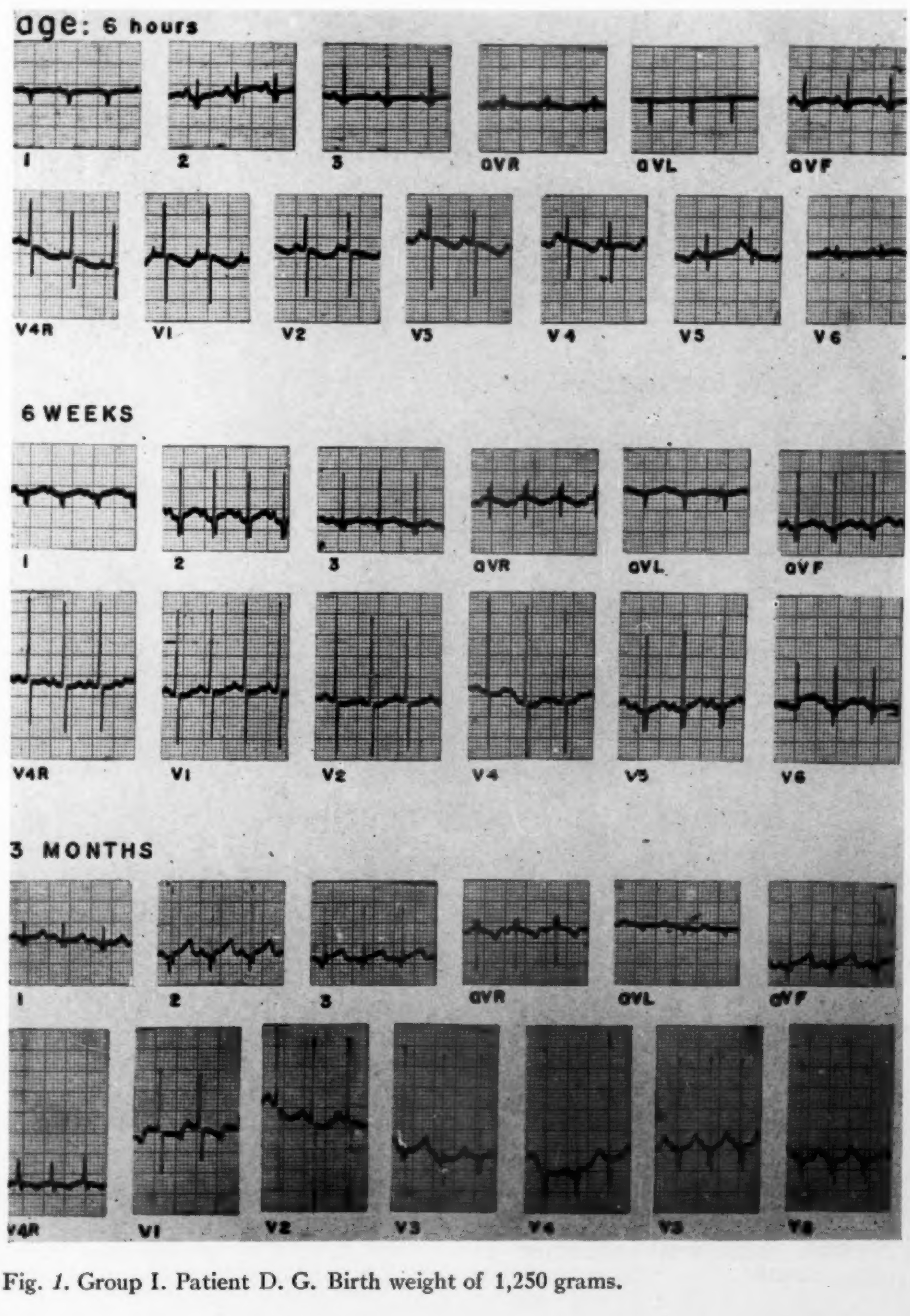

Fig. *1*. Group I. Patient D. G. Birth weight of 1,250 grams.

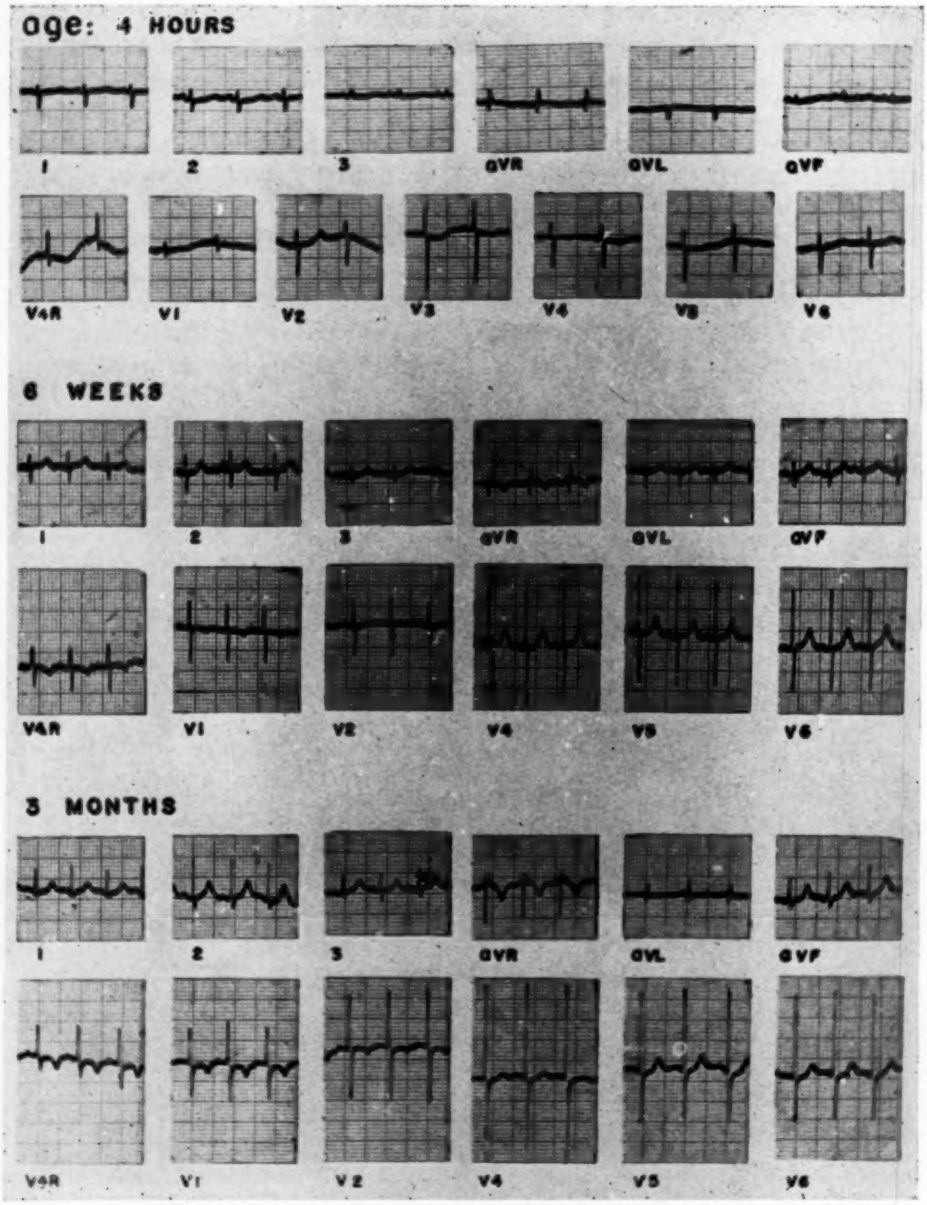

Fig. 2. Group II. Patient K. G. Birth weight of 1,754 grams.

Heck[14] gave a shorter P-R interval, 0.092 second at 1 day of age in his premature infants.

The P waves were usually peaked with voltage up to 2.5 or 3.0 mm. on the first day of life, with a duration of 0.05 and 0.07 second. The so-called "P" pulmonale on the first day of life may have represented higher pressures in the pulmonic circuit which are reflected in the atria. The axis of the P wave is very constant at 60 degrees. There was little variation at any age and weight. This was confirmed in earlier studies.[11,12,14]

The Q-T interval on the first day of life was slightly prolonged. Body temperature did not play a great part in this, because all of the premature babies studied had stabilized body temperature above 37°C. There are many factors which may prolong the Q-T interval, among which are hypocalcemia and anoxia as well as hypothermia.[8,18] Therefore, a prolonged Q-T interval may occur with a normal QRS interval or with a prolonged QRS interval.[18] In these cases the QRS interval on the first day of life was not prolonged, indicating that a change had occurred in

the time that it took the stimulated ventricles to return to the resting state.

The mean manifest electrical axis of the QRS complex measured in the frontal plane followed the same pattern as that found in earlier studies.[2,6,12-14] There was no essential difference in any of the weight groups studied on the first day of life. There was a change in mean ÂQRS, with a shift to the left at 6 weeks and a small shift at 3 months.

The measurements of the height of the R waves in Leads V_{4R}, V_1, and V_6, as well as the R/S ratio in Leads V_{4R} and V_1, and the total of the R+S waves measured in its greatest height in Leads V_2 and V_4 will be most helpful in the diagnosis of right ventricular hypertrophy in the newborn premature infant. It was apparent from this study that a well-formed R wave was present in Lead V_6 on the first day and was of equal height with that found in Lead V_{4R}, and that the R wave was taller in Lead V_1. The S wave increased in Lead V_{4R} as the infant grew from birth to 3 months of age.

In an earlier study[5] of the ECG of the newborn full-term infant it was noted that the R/S ratio in the right precordial leads was less than 1 in a number of the infants

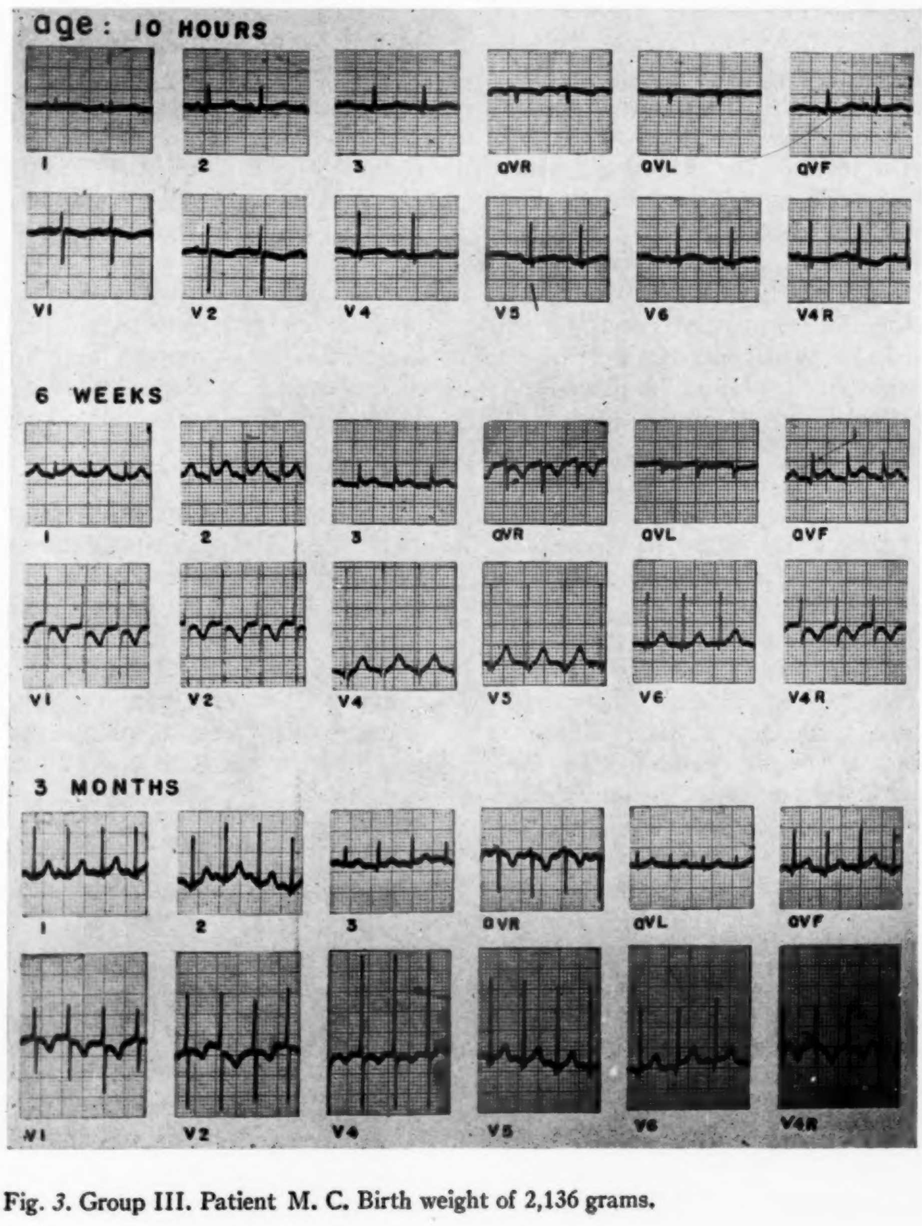

Fig. 3. Group III. Patient M. C. Birth weight of 2,136 grams.

studied. In premature infants this pattern also was found in a significant percentage of the infants studied on the first day of life, and it was noted that the R/S ratio more nearly approached 1.0 as these infants grew older. The R wave was well developed in Lead V_6 on the first day of life and indicated a difference from that of full-term infants at that age. De la Cruz (cited by Sodi-Pallares and associates[17]) studied 70 normal hearts of infants and children who ranged in age from 6 months of intrauterine life to 11 years and showed that the thickness of the free wall of the right ventricle is less than that of the left ventricle. These anatomic findings are not contrary to the morphology recorded in right (V_{4R}, V_1, V_2) and left (V_5 and V_6) precordial leads in these premature infants.

The greatest total voltage of R+S measured in Lead V_2 to Lead V_4 never approached the level of the pathologic which had been found in an earlier study on ventricular septal defects.[19]

It was stated in an earlier study[17] that the T waves are upright in the right precordial leads and frequently inverted in the left precordial leads during the first hours, or in the first days, of life. In this study, in the smallest group of premature infants (weight of 800-1,300 grams) no ECG was found that had upright T waves in the right precordial leads nor inverted T waves in the left precordial leads. In the second group of infants (Group IIA, weight of 1,300-1,800 grams), only 3 per cent had upright T waves in the right precordial leads during the first 24 hours of life; none of these infants had inverted T waves in the left precordial leads. In the infants who ranged in weight between 1,800 and 2,300 grams, 13 per cent had upright T waves in the right precordial leads and none had inverted T waves in the left precordial leads. By 6 weeks of age there was a change in all of the electrocardiograms to inverted T waves in the right precordial leads. In a screening study done on normal premature infants of all weights, those infants who had had upright T waves in the right precordial leads on the first day of life all showed normally inverted T waves by the third day of life.[20] This finding agreed with the results of the earlier studies of European workers.[11,12]

Summary and Conclusions

1. Electrocardiograms were taken on 143 normal premature infants on the first day of life, at 6 weeks, and again at 3 months. The infants were divided into three groups, on the basis of their weight at birth.

2. All patients had normal sinus rhythm at an average rate of 140. The mean P-R interval was 0.11 second, and the mean duration of QRS was between 0.36 and 0.40 second. The $\hat{A}P$ was +60 degrees. These findings were independent of birth weight and were unchanged from birth to 3 months of age.

3. The $\hat{A}QRS$ was greater than +100 degrees at birth and showed a progressive leftward shift with age in all three groups. This leftward shift was also evidenced by: (a) the increasing amplitude of the S wave in Lead V_{4R} with age, (b) the decreasing R/S ratio in the right precordial leads with age, and (c) the well-developed R wave in Lead V_6 which increased in amplitude with age.

4. There was a significant group of infants (38 per cent of the whole study material) who showed at birth an R/S ratio of less than 1 in the right precordial leads. With age this ratio tended to increase rather than decrease.

5. The T wave in the left precordial leads was uniformly upright in all patients at all ages. The majority of patients showed inverted T waves in the right precordial leads at birth, and this too did not change up to 3 months of age. Thirteen patients (1 in Group II and 12 in Group III) showed upright T waves in the right precordial leads which then subsequently inverted in all of these patients by 6 weeks of age.

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Effects of posture, upright exercise, and myocardial stimulation on cardiac output in patients with diseases affecting diastolic filling and effective systolic ejection of the left ventricle

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Two patterns of cardiovascular responses to upright exercise of walking were found in previous studies of patients with heart diseases.[1] The majority of individuals tested showed increases in heart rate, cardiac output, mean systemic arterial pressure, and arteriovenous oxygen difference as compared with the resting values observed when they were either recumbent or sitting upright. A minority of patients exhibited a faster heart rate, but less increase in cardiac output, because of a failure to raise stroke index above the sitting level; this was associated with a fall in arterial blood pressure designated as "exertional hypotension." Both groups of patients had a significant fall in stroke volume when they changed posture from supine to sitting upright. The effects of pathologic lesions primarily altering either diastolic filling or effective systolic ejection of the left ventricle have been investigated in further studies on comparative response to postural changes, upright exercise, and myocardial stimulation. In this connection, effective systolic ejection refers to the net forward flow through the aorta.

Circulatory adaptations to upright posture were described by McMichael and Sharpey-Schafer[2] in 1944. Although oxygen consumption increased slightly during standing, arteriovenous oxygen difference widened, and cardiac output fell 25 per cent from a mean value during recumbency of 6.0 L./min. to a mean of 4.5 L./min.[2] More recently, Novy and associates[3] reported even greater decreases in cardiac output on motionless standing for 10 minutes. Presumably, these changes represent a redistribution of blood volume (which diminishes the pulmonary and increases the systemic venous reservoirs) in response to the stress of gravity in relation to the position of the body. Rushmer[4] has emphasized the importance of these postural changes in the evaluation of ventricular function during exercise in the erect position.

Although hyperkinemic responses to exercise have usually been attributed to

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increases in both heart rate and stroke volume, Rushmer recently has questioned the capacity of the stroke volume to increase above the resting recumbent value.[5] In human subjects, however, Musshoff and associates[6] found both stroke volume and heart rate increased progressively with graded amounts of exercise performed during recumbency. Mitchell and associates,[7] in studies of maximal oxygen consumption in normal subjects during exercise in the upright position, found that both stroke volume and heart rate virtually doubled when compared with values obtained with the subjects standing at rest. Cross-circulation experiments in dogs have identified both neural and humoral mechanisms for the hyperkinemia of exertion.[8] With respect to humoral agents, however, norepinephrine has been found to be significantly increased only at maximal work loads in human beings.[9]

Since the synthetic catecholamine, isoproterenol, is more potent than either epinephrine or norepinephrine in increasing heart rate and contractile force in the isolated, perfused heart of several mammalian species,[10] it is an effective myocardial stimulant. It restores rhythmicity after reflexly induced standstill and accelerates ventricular rate in the presence of complete atrioventricular block.[11] It produces tachycardia in the intact dog, whereas comparable doses of epinephrine or norepinephrine produce bradycardia.[12] In the isolated, perfused canine heart, isoproterenol increases myocardial oxygen consumption without depleting stores of glycogen when employed in very minute doses that do not induce arrhythmias.[13] In human subjects, isoproterenol increases cardiac output and lowers pulmonary "capillary" pressure even in patients with congestive heart failure.[14] It increases stroke volume significantly ($p < .02$) in normal subjects in the supine position, but less so ($p > .05$) when the head is tilted up 60 degrees.[15] Peripheral venous constriction with isoproterenol tends to redistribute blood volume from systemic to pulmonary venous reservoirs[16] and contributes to an increased "central blood volume."[17] Since with progressively larger doses, isoproterenol produces arrhythmias, conduction defects,[13] and myocardial necrosis,[18] the use of this drug to stimulate the myocardium must be carefully supervised.

Material and methods

Fourteen patients with diseases affecting the chambers of the left side of the heart were studied in conjunction with diagnostic cardiac catheterization. Of the 8 females and 6 males, 7 patients had limitation of diastolic filling of the left ventricle due to mitral stenosis (confirmed surgically in all 6 who were operated upon), and 7 had lesions which reduced the effective systolic ejection of the left ventricle. Of the latter patients, 2 had predominant mitral regurgitation, 2 had aortic stenosis, and 1 each had aortic regurgitation, multivalvular rheumatic heart disease (without significant mitral stenosis), and hypertensive cardiovascular disease. Atrial fibrillation was present in 5 patients with mitral stenosis and in 2 with left ventricular diseases. All except 2 patients, one with aortic stenosis and another with mitral stenosis, were taking digitalis. The average functional capacity (Classes I to IV of the New York Heart Association) and physical fitness index of tolerance for a standardized exercise test[19] were 3.0 and 7.1, respectively, for patients with mitral stenosis, and 2.3 and 14.5, respectively, for patients with left ventricular disease. Thus, patients with mitral stenosis selected for this study tended to be more impaired both clinically and by exercise testing than the other patients.

Normal saline was injected subcutaneously for placebo sedation, and 2 per cent procaine was infiltrated for local anesthesia at the site of arterial and venous cut-downs. Arterial pressure and blood samples were obtained by a PE 90 polyethylene catheter inserted into the lumen of the radial artery; a No. 6F cardiac catheter was guided into the right pulmonary artery. Pressures were recorded with a Statham P23D transducer and Sanborn polygraph. Pressures were recorded continuously except during intermittent sampling and flushing of the catheters.

The oxygen content of samples of blood was determined by the method of Van Slyke-Neill. Oxygen consumption, and ventilation were recorded while breathing oxygen with a 13.5-liter Collins respirom-

$$(1)\ \text{Resistance Index (dynes sec. cm.}^{-5}\times \text{M.}^2) = \frac{(\textit{Mean Pressure})\ (1.332)\ (60)}{\textit{Cardiac Index}}$$

$$(2)\ \text{LV work (Kg.M./min./M.}^2) = \frac{(\textit{Cardiac Index})\ (1.065)\ (P_{S_A} - 5)\ (13.6)}{1{,}000}$$

eter. Cardiac output was determined by the direct Fick principle, utilizing blood withdrawn from the pulmonary artery for the determination of mixed venous oxygen content. Arterial samples were withdrawn simultaneously from the radial artery.

Each patient served as his own control, and responses to posture, isoproterenol, and exercise were determined. Five per cent dextrose in water was slowly infused intravenously; when a steady state was assured, initial control measurements were made while the subject was supine. Afterward, another solution containing 0.4 micrograms per milliliter of isoproterenol* was administered at a rate of from 50 to 120 drops per minute (.02 to .04 μg/Kg./min.). Facial flushing, hyperventilation, precordial pounding, or occasional tremulousness occurred in a few subjects within a minute or two, and usually were accompanied by tachycardia and increased arterial pulse pressure. After 4 to 7 minutes, when a steady state was apparent by inspection of the spirogram and recordings of arterial pressure, samples of blood were drawn for determination of oxygen content. As judged by inspection of the heart rate and pulse pressure, the effects of isoproterenol disappeared within 5 minutes after the infusion was stopped. Under these conditions there were no adverse clinical effects with this drug.

After 25 to 40 minutes, additional control observations were made in 9 patients after they had been sitting in a chair for several minutes. Then each subject walked on a treadmill at a rate of 1.7 miles per hour at a 10 per cent grade of incline. After 4 minutes of steady-state exercise, samples of blood were withdrawn, and ventilation and oxygen consumption were recorded for another determination of cardiac output.

In five instances the subjects were exercised first, and the observations with isoproterenol were made several minutes later, with no discernible difference in results due to this change in experimental procedure.

*Isuprel, Winthrop-Stearns.

When the subjects were supine, the zero reference was placed at 10 cm. above the table; when they were upright, it was reset at the level of the fourth rib anteriorly. Arterial pressures were integrated planimetrically or electrically; total pulmonary and systemic resistance indices were computed by formula 1 (top of page). Apparent left ventricular work* was estimated by formula 2 (top of page), where 1.065 = specific gravity of whole blood, P_{S_A} = mean systemic arterial pressure, and 13.6 = specific gravity of mercury. Apparent stroke work of the left ventricle was derived by dividing the foregoing value by the heart rate.

All data were processed in an IBM 650 digital computer to derive means, standard deviations, and 1,080 cross-correlations by the product-moment method.

Results

A statistical analysis of the mean responses of two types of patients with left-heart diseases to three different experimental procedures is presented in Table I. The salient differences between these two types of patients, as well as the significant changes common to both, are listed in Table II. Average responses of the components of cardiac output to the stress of exercise in the upright position are shown in Fig. 1.

I. Hemodynamic observations in patients resting in the supine position. The 7 patients with left ventricular diseases had virtually normal pressure and flow measurements while resting in the recumbent position, except for 1 individual with a slight elevation of the wedged pulmonary arterial

*Calculations of left ventricular work for the patients with aortic valvular disease were not based upon the actual pressure within the left ventricle; similarly, the volume of regurgitant flow was not determined.

(PC) pressure. Hence, none of the other 6 patients had significant evidence of left ventricular failure by these criteria.

All 7 patients with mitral stenosis had a moderate, but definite, increase in PC pressure. Ventilation, pulmonary arterial pressure, and total pulmonary resistance tended to be higher, just as the cardiac and stroke indices tended to be lower in patients with mitral stenosis than in patients with left ventricular diseases. These differences were not significant ($p > .05$) because of appreciable variation for the small number of patients involved in this study. However, ventilation varied inversely with stroke index ($r = -0.94$) and directly with total pulmonary resistance ($r = +0.95$) in mitral stenosis but not in those with left ventricular diseases ($r = -0.14$ and -0.10, respectively). The lower arterial oxygen content in the patients with mitral stenosis was related to a lower hemoglobin concentration.

II. Effects of isoproterenol in patients in the supine position. Intravenous infusion of isoproterenol produced hyperkinemia, systemic vasodilatation, and mild hyperventilation in both types of patients. The high output state was achieved primarily by acceleration of heart rate. Since the increased cardiac index was in excess of metabolic demands for oxygen consumption, the arteriovenous oxygen difference diminished. Despite the fall in systemic resistance, the apparent work of the left ventricle was increased, largely as a result of the moderate tachycardia.

All patients with left ventricular diseases and 5 of the 7 with mitral stenosis showed a fall in total pulmonary resistance. Patients with mitral stenosis showed a greater increase in oxygen consumption, presumably reflecting increased work of the right ventricle against augmented pulmonary arterial pressure as well as the increased work of breathing. In the two instances in which changes in PC pressure were observed in patients with mitral stenosis, it increased from 23 to 28, and from 24 to 45 mm. Hg in response to isoproterenol.

III. Effects of sitting upright. Both types of patients showed a significant fall in stroke index. Since the heart rate accelerated slightly, this prevented a corresponding fall in cardiac index. Nevertheless, arteriovenous oxygen difference widened, and oxygen consumption increased slightly. Presumably, these changes reflected an alteration in the distribution of the blood volume imposed by the change in the position of the body with respect to gravitational force, and a slight increase in metabolic activity of the muscles maintaining this posture. Despite the probable reduction of blood volume in the thorax, mean pulmonary arterial pressure increased slightly. Possibly, the latter change represented an error in estimation of the zero reference level under these conditions. There were then no significant changes with posture unique to either type of patient, but the arteriovenous oxygen difference varied inversely with the cardiac index ($r = -.92$) only in patients with left ventricular diseases (vs. $r = -.21$ in those with mitral stenosis).

IV. Effects of exercise on patients in the upright position. Both types of patients exhibited marked increases in oxygen consumption and ventilation as a result of the enhanced metabolic activity in the exercising skeletal muscles. The augmented oxygen transport was achieved by a substantial increase in both cardiac index and arteriovenous oxygen difference. The former resulted primarily from an acceleration of heart rate. Apparent left ventricular work was raised accordingly, although a slight increase in stroke work was contributory in patients with left ventricular diseases. The fall in systemic resistance probably represented vasodilation, accom-

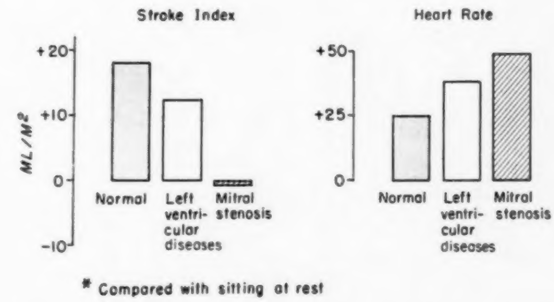

Fig. *1.* Cardiac adaptations to exercise in upright position in terms of average changes in stroke index and heart rate, as compared with sitting at rest, in normal subjects and patients with either left ventricular diseases or mitral stenosis. (See text for details.)

Table I. *Mean values ± standard deviations*

	Left ventricular diseases ($N = 7$)				*Mitral stenosis* ($N = 7$)			
	Supine	*Isoproterenol*	*Sitting*	*Walking*	*Supine*	*Isoproterenol*	*Sitting*	*Walking*
Ventilation (L./min.)	8.0 ± 1.6	13.3 ± 4.5**	9.9 ± 1.9*	25.2 ± 5.2†††	10.6 ± 6.8	17.8 ± 8.9	13.3 ± 7.1	31.7 ± 10.4†††
O_2 consumption (ml./M.²/min.)	132.6 ± 16.3	137.5 ± 68.6	155.5 ± 11.2**	509.4 ± 66.5†††	118.6 ± 27.8	177.3 ± 45.0**	138.7 ± 29.9	401.4 ± 138.3†††
Arterial O_2 content (vol. %)	19.9 ± 1.9	19.8 ± 1.9	20.1 ± 1.8	20.5 ± 1.8	17.9 ± 1.5	18.2 ± 1.6	18.3 ± 1.2	18.9 ± 1.2
Mixed venous O_2 content (vol. %)	15.1 ± 2.5	16.5 ± 2.2	13.6 ± 1.6	9.3 ± 3.3†††	12.9 ± 1.5	13.6 ± 2.1	12.2 ± 0.9	7.3 ± 0.7†††
A-V O_2 difference (ml./L.)	48.4 ± 13.7	33.6 ± 6.8*	66.6 ± 11.9	112.3 ± 18.0†††	49.2 ± 10.5	45.6 ± 10.6	60.8 ± 7.4	115.9 ± 12.7†††
Cardiac index (L./M.²/min.)	3.0 ± 1.0	5.0 ± 1.3**	2.5 ± 0.9	4.7 ± 0.9†††	2.5 ± 0.7	4.2 ± 1.8*	2.3 ± 0.5	3.5 ± 1.4†
Heart rate	66.4 ± 14.9	94.0 ± 27.6*	77.2 ± 12.0	115.5 ± 34.3††	73 4 ± 19.0	114.6 ± 42.4*	88.6 ± 23.5	137.7 ± 28.9†††
Stroke index (ml./M.²)	46.0 ± 13.7	58.0 ± 16.9	31.8 ± 7.5*	44.5 ± 15.7	36.0 ± 9.7	44.0 ± 22.4	28.0 ± 8.7	27.7 ± 14.7
Mean PA pressure (mm. Hg)	18.9 ± 3.8	16.5 ± 12.3	20.5 ± 3.2	29.3 ± 4.1†††	29.9 ± 7.5	43.3 ± 22.1	32.1 ± 10.1	47.7 ± 20.2
Mean systemic arterial pressure (mm. Hg)	100.9 ± 13.3	90.0 ± 20.4	116.6 ± 18.1	123.3 ± 16.5	96.3 ± 12.4	103.0 ± 19.2	114.0 ± 23.0	113.1 ± 25.9
Total pulmonary resistance (dynes sec. cm.$^{-5}$M.²)	547 ± 27	270 ± 138***	718 ± 256	540 ± 200	1,063 ± 483	946 ± 762	1,246 ± 643	1,246 ± 634
Systemic resistance (dynes sec. cm.$^{-5}$M.²)	3,014 ± 1,094	1,231 ± 535***	4,057 ± 1,250	2,177 ± 181	3,386 ± 1,221	2,259 ± 1,207	4,179 ± 1,299	3,027 ± 1,597
LV work (Kg.M./min./M.²)‡	4.12 ± 1.16	6.38 ± 2.49*	3.97 ± 0.55	8.11 ± 2.39†††	3.30 ± 0.94	5.92 ± 2.73*	3.63 ± 0.92	5.45 ± 2.45
LV stroke work (Kg.M./beat/M.²)‡	.065 ± .023	.074 ± .035	.052 ± .016	.072 ± .039	.047 ± .014	.062 ± .037	.046 ± .020	.044 ± .025

*Probability of change from resting supine value being <.05; ** <.01; *** <.001.
†Probability of change from resting sitting value being <.05; †† <.01; ††† <.001.
‡Apparent left ventricular work per minute and per heart beat.

Table II. Average magnitude of significant differences with types of disease and changes with experimental procedures ($p < .05$)

Type of left heart disease	Experimental procedure	Number of observations	Variable	Average difference or change	Average % difference or % change	p
Mitral stenosis	Supine, control	7	Mean PA pressure	+11 mm. Hg	58	<.001
(vs. LV diseases)	Supine, control	7	Arterial O_2 content	−2.0 vol. %	− 10	<.01
Left ventricular diseases	Isoproterenol (vs. lying supine)	7	Total pulmonary resistance	−277 dynes sec. cm.$^{-5}$M.^{2}	− 51	<.001
		7	Systemic resistance	−1,880 dynes sec. cm.$^{-5}$M.^{2}	− 62	<.001
		7	Ventilation	+5.3 L./min.	+ 66	<.01
		7	AV O_2 difference	−14.8 ml./L.	− 31	<.02
	Exercise (vs. sitting upright)	7	LV work (apparent)	+4.0 Kg.M./min./M.^{2}	+102	<.001
		7	Systemic resistance	−1,880 dynes sec. cm.$^{-5}$M.^{2}	− 46	<.001
		7	Mean PA pressure	+9 mm. Hg	+ 43	<.001
Mitral stenosis	Isoproterenol (vs. lying supine)	7	Oxygen consumption	+59 ml./M.^{2}/min.	+ 50	<.01
Both types	Sitting upright (vs. lying supine)	14	Stroke index	−11 ml./M.^{2}	− 27	<.001
		14	AV O_2 difference	+14.9 ml./L.	+ 31	<.001
		14	Mean PA pressure	+17 mm. Hg	+ 17	<.02
		14	Oxygen consumption	+21 ml./M.^{2}/min.	+ 17	<.03
	Isoproterenol (vs. lying supine)	14	Cardiac index	+1.87 L./M.^{2}/min.	+ 68	<.001
		14	Systemic resistance	−1,460 dynes sec. cm.$^{-5}$M.^{2}	− 45	<.001
		14	Heart rate	+34	+ 49	<.003
		14	LV work (apparent)	+2.4 Kg.M./min./M.^{2}	+ 65	<.003
		14	Mixed venous O_2 content	+2.15 vol. %	+ 15	<.01
		14	AV O_2 difference	−9.16 ml./L.	− 19	<.03
		14	Ventilation	+6.2 L./min.	+ 68	<.02
	Exercise (vs. sitting upright)	14	Oxygen consumption	+308 ml./M.^{2}/min.	+210	<.001
		14	Ventilation	+16.8 L./min.	+145	<.001
		14	AV O_2 difference	+50.4 ml./L.	+ 79	<.001
		14	Mixed venous O_2 content	−4.55 vol. %	− 35	<.001
		14	LV work (apparent)	+2.98 Kg.M./min./M.^{2}	+ 78	<.001
		14	Cardiac index	+1.72 L./min./M.^{2}	+ 72	<.001
		14	Heart rate	+44	+ 53	<.001
		14	Systemic resistance	−1,520 dynes sec. cm.$^{-5}$M.^{2}	− 37	<.002
		14	Mean PA pressure	+12 mm. Hg	+ 46	<.03

panying the increased flow. Mean pulmonary arterial pressure rose somewhat, especially in patients with mitral stenosis. Radial arterial pressure was not significantly altered in either group, but tended to rise in those with left ventricular diseases and to fall in the individuals with mitral stenosis.

Discussion

Both normal subjects and cardiac patients exhibit a fall in stroke volume and cardiac output when they change from the supine position to sitting upright. Inasmuch as estimates of the "central blood volume" have revealed a corresponding decrease with this change in posture,[20] it is likely that there was a proportionate reduction in atrial volumes, and, in turn, the diastolic filling volumes of the ventricles. Thus, these changes in blood flow with changes in posture are compatible with the Starling hypothesis that the "amount put out at each beat depends directly on the diastolic filling."[21]

Myocardial stimulation with isoproterenol produced more acceleration of heart rate in the cardiac than in the normal subjects.[15] Indeed, in patients with mitral stenosis there was an even greater positive chronotropic response as well as a smaller positive inotropic response in stroke index. Statistically, normal subjects were reported[15] to increase stroke index significantly ($p < .02$), but neither type of cardiac patient reported here showed a significant increase ($p > .1$). This response undoubtedly varies with the quantity of drug administered and with the selection of cardiac patients made, for previous studies[17] on patients with left ventricular diseases have demonstrated a small rise in stroke index with isoproterenol ($p < .03$). Because of the faster heart rate in cardiac patients reported here, changes in left ventricular work per minute and systemic resistance during infusion with isoproterenol were similar to those observed in normal subjects.

Total pulmonary resistance diminished during infusions of isoproterenol in patients with left ventricular diseases. In a few instances in which changes in PC pressure were measured, there was a decrease in these patients in contrast to a rise in those with mitral stenosis, in whom the stenotic lesion produced a relatively fixed resistance to filling of the left ventricle. Hence, the increased pulmonary "capillary" pressure was a result of increased flow through a small mitral orifice. Ventilation in patients with mitral stenosis also tended to be higher with isoproterenol than in patients with left ventricular diseases. It should be noted, however, that in the making of these comparisons with left ventricular diseases, the observations were based upon patients who did not exhibit pulmonary hypertension secondary to left ventricular failure.

Exercise in the upright posture produced the expected increase in oxygen consumption and rise in ventilation, heart rate, cardiac index and left ventricular work, as well as widening of the arteriovenous oxygen difference. Systemic resistance diminished as blood flow increased. In contrast to the findings in normal subjects,[22] stroke index showed only a small average increase above the resting value when the subjects were seated (Fig. 1). Despite greater acceleration of heart rate, cardiac index did not increase as much in these cardiac patients as in normal subjects performing a comparable amount of work on the treadmill.[22]

Patients with mitral stenosis differed from those with left ventricular diseases in their responses to exercise, in that the average stroke volume did not increase above the resting value while they were seated. Also in the patients with mitral stenosis, mean systemic arterial pressure failed to increase. This phenomenon of "exertional hypotension" was described previously in association with the inability to increase stroke index with exertion above the level found in the upright posture at rest.[1] Thus, the capacity to increase the effective stroke output with exertion was quantitatively more impaired in patients with mitral stenosis who had high resistance to diastolic filling of the left ventricle. The other components of oxygen transport, namely, heart rate and arteriovenous oxygen difference, were not limited, but rather tended to exhibit compensatory increases above the normal range. With exercise, however, pulmonary arterial pressure increased in all instances, whereas total pulmonary resistance exhibited a

wide range of responses. Since the "PC" pressure was not recorded under this experimental condition, no inference could be made with regard to changes in vascular resistance.

Ventilation increased in response to isoproterenol. This was a significant change in patients with left ventricular diseases, and not associated with any rise in pulmonary arterial pressure. In patients with mitral stenosis who also had some pulmonary vascular engorgement, increases in ventilation were correlated with a rise in pulmonary arterial pressure under all experimental circumstances (r ranged from +0.68 to +0.85). Whereas the ventilatory response could be mediated primarily by central neurogenic mechanisms, it was possibly enhanced by stimulation of pulmonary stretch reflexes in patients with mitral stenosis.

Cardiac index was correlated with oxygen consumption in all 14 patients (r varied from +0.54 during isoproterenol to +0.86 during walking). Hence, regulation of cardiac output was determined largely by metabolic activity, as reflected in the total body oxygen consumption. Undoubtedly, it was modified in accord with Starling's concepts by the effects of changes on the distribution of blood volume available for diastolic filling of the ventricles. Under special circumstances it was predominantly affected by myocardial stimulation. Finally, in these patients with cardiovascular diseases, regulation was altered by pathologic mechanisms affecting diastolic filling and effective systolic ejection of the left ventricle. Although stroke index correlated with cardiac index (r ranged from +0.68 to +0.90), heart rate was not related to cardiac index during recumbency, isoproterenol, or sitting (r = −0.39 to +0.07), but was inversely related during walking (r = −0.59). This lack of a direct relationship is attributed to the excessive increase in heart rate, as a compensatory mechanism for approaching a more nearly adequate cardiac output relative to the metabolic requirements of the body. Thus, when the capacity to increase stroke index is impaired by disease, a relative tachycardia is the only compensatory response available to the heart. If the available acceleration of heart rate is insufficient to produce the necessary flow of blood to meet the metabolic requirements of the peripheral tissues, further increases in arteriovenous oxygen difference, or rate of oxygen extraction from the available blood flow, ensue. Failure of these mechanisms initiates a compensatory increase in anaerobic metabolism at the cellular level.[23]

Summary

1. Cardiovascular responses to changes in posture, exercise in the upright position, and myocardial stimulation with isoproterenol have been studied in 14 patients with diseases of the left side of the heart. Seven patients had limitations of diastolic filling of the left ventricle imposed by mitral stenosis, and 7 patients had lesions which reduced the effective systolic ejection of the left ventricle.

2. In both types of patients, stroke index fell and arteriovenous oxygen difference widened significantly with a change in posture from supine to sitting upright.

3. The mean values during rest in the recumbent position were virtually normal for patients with left ventricular diseases. Although heart rate and cardiac index increased significantly with the exertion of walking, stroke index increased toward, but not above, the resting supine value, and the mean arterial pressure, on the average, increased slightly.

4. Patients with mitral stenosis tended to have lower stroke and cardiac indices and higher pulmonary arterial pressure and ventilation during rest in the recumbent position. Cardiac index was increased by the exertion of walking, largely because of a disproportionate acceleration of heart rate; stroke index, on the average, showed no increase above the lowered value produced by the patient's sitting upright. The average systemic arterial pressure for these patients did not rise.

5. Myocardial stimulation with isoproterenol during recumbency significantly increased heart rate, cardiac index, and left ventricular work, and lowered systemic arterial resistance in both types of patients. Except in 2 patients with pulmonary vascular disease, total pulmonary resistance diminished.

6. A primary defect of patients with diseases of the left side of the heart is an

impaired capacity to increase stroke output in response to exertion or to myocardial stimulation. This may result from a number of mechanisms distorting effective systolic ejection; such capacity is particularly restricted by lesions, such as mitral stenosis, that offer increased resistance to diastolic filling of the left ventricle. Compensatory mechanisms include tachycardia, widening of the arteriovenous oxygen difference, and anaerobic metabolism.

7. There was a significant correlation in patients with mitral stenosis between minute ventilation and pulmonary arterial pressure under each experimental state.

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The value of the apexcardiogram as a reference tracing in phonocardiography

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The growing importance of phonocardiography as a diagnostic tool has emphasized the need for a simpler and better reference tracing. Indirect arterial tracings,[1-4] carotid and peripheral (femoral,[5] brachial, and radial) are of aid in identifying the aortic and pulmonic components of the second sound but they are of no value in the identification of the diastolic events of the cardiac cycle. The jugular venous tracing is the best reference tracing available to identify the events from the right side of the heart, as has been recently emphasized by Hartman.[6] The time lag from the right auricle to the jugular vein, with the present type of recording devices, seems to be negligible. However, only indirectly does the jugular venous pulse give information of the events in the left side of the heart.[3,6]

Since 1957, we have been recording the movements of the chest wall overlying the left and right ventricles and designating the tracings as the apexcardiogram (ACG).[7] With careful attention to detail, and in certain specific conditions, the activity of the two ventricles can be separated: the right and left apexcardiogram. Hartman,[8] prior to this time, had established the value of this measurement.

Material and method

The present report is based on our experience with over 1,200 patients in whom the ACG was recorded. In over 200 patients the ACG was obtained before and after heart operation for correction of various congenital and acquired malformations of the left and right sides of the heart.

In the great majority of our patients the clinical diagnosis was confirmed by right or left heart catheterization, cineangiocardiography, and dye-dilution studies, as well as operation or postmortem examination. All the tracings in this report were recorded from patients with diagnoses proved by cardiac catheterization or operation.

The equipment used for recording the phonocardiograms and apexcardiograms was the Sanborn Twin-Beam phonocardiograph with a Sanborn microphone (62-1500-C 13). The paper speed was 75 mm. per second. The ACG was recorded using a pulse crystal microphone (Sanborn #374) which reproduces an electrical signal proportional to changes in pressure in the tubing. Frequency response of this crystal microphone is from 1 to 1,000 cycles per second. Detailed study of the electronic characteristics of this system has been

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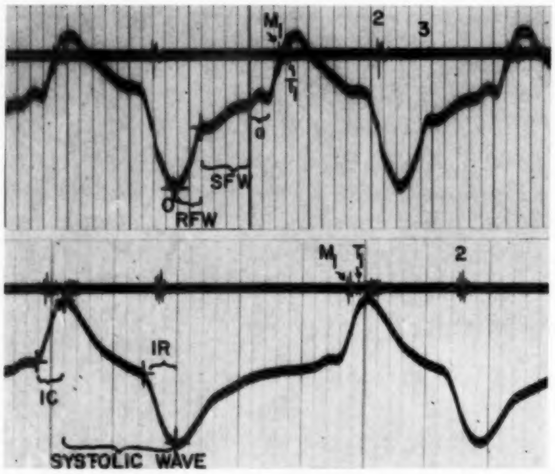

Fig. *1*. Apexcardiogram of the left ventricle. Normal subject. Split first sound in both tracings occurring before the peak of the systolic wave. Components of the apexcardiogram as described in the text. *IC*, Isometric contraction. *IR*, Isometric relaxation. *RFW*, Rapid filling wave. *SFW*, Slow filling wave. "*a*," Atrial wave.

described by Miller and White.[9] After completion of the routine PCG, the point of maximal impulse with the patient in the left lateral decubitus position was determined by palpation, and a left ventricular complex was confirmed on the electrocardiogram from this point. The sound microphone was then positioned so that the pick-up bell with side opening tube was placed directly over the point of maximal impulse, and the ACG was recorded simultaneously with the PCG. When it was desirable to have the microphone at a different auscultatory area that was not the apex, a funnel-type of cup applicator (as used to record the indirect carotid tracing) was used. The tracings were recorded in mid-expiration. The technique to record the right ventricular ACG* was essentially the same as described above, except that the pick-up bell or the cup applicator was placed at the left sternal border, fourth or fifth intercostal space, and a right ventricular electrocardiographic complex was recorded from this area.

The following abbreviations have been employed in this report: *1*, first sound; *2*, second sound; *3*, third sound; *4*, fourth sound; A_2, aortic valve closure; P_2, pulmonic valve closure; *OS*, opening snap; *SM*, systolic murmur; *DM*, diastolic murmur; *ASM*, atrial systolic murmur; *ACG*, apexcardiogram; *O-point*, beginning of filling wave; *RFW*, rapid filling wave; *SFW*, slow filling wave; *IC*, isometric contraction; *IR*, isometric relaxation; "*a*", atrial wave. Vertical lines in the tracings are 0.04 second apart. In several patients, the ACG was recorded during right or left heart catheterization with simultaneous atrial and ventricular pressure curves. In these circumstances, the ACG was recorded with the Sanborn Poly-Viso.

*The term *right ventricular apexcardiogram* is not ideal to describe the tracings recorded at LSB-4th ICS, which represents the movement of the body of the right ventricle rather than the apex. However, the terminology is well known and we have used it simply because it has background and in general is understood.

Normal apexcardiogram

A normal ACG presents the following waves: "*a*" *waves*, due to atrial contraction; *systolic wave*, due to ventricular contraction; *rapid filling wave* (*RFW*), due to rapid early diastolic filling; *slow filling wave* (*SFW*), follows the RFW and ends at the level of the *a* wave, representing the slow ventricular filling (see Fig. 1).

After the atrial contraction represented by an "a" wave which is coincident with

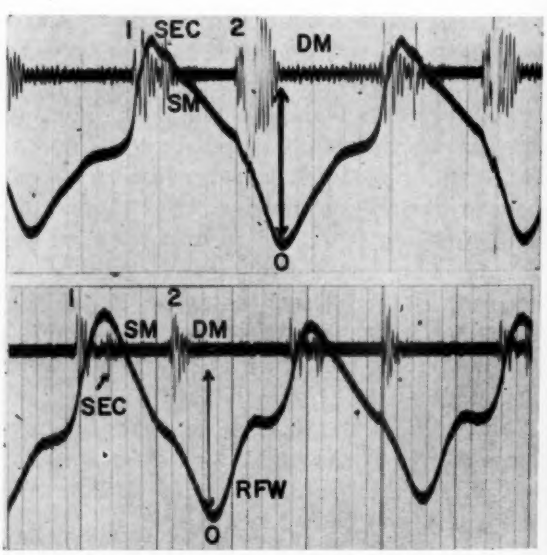

Fig. *2*. Apexcardiogram of the right ventricle. Two cases of ventricular septal defect with severe pulmonary hypertension. Note the presence of systolic ejection click which follows the peak of the systolic wave by 0.03 to 0.04 second. Observe the diastolic murmur of pulmonary insufficiency starting before the O-point. The phonocardiograms were recorded at the left sternal border, fourth intercostal space, with logarithmic technique. Compare with Fig. 1.

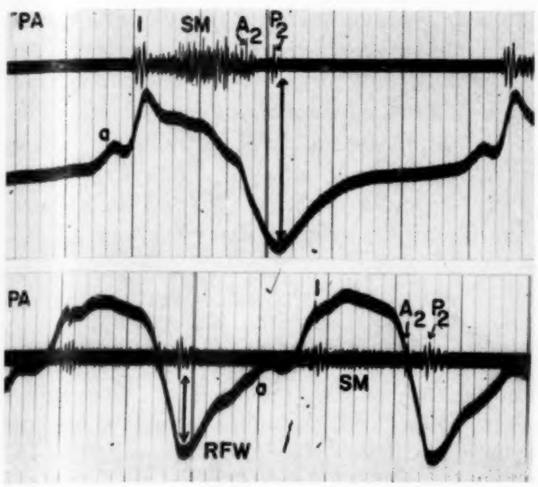

Fig. 3. Apexcardiogram of the right ventricle. *Top:* Pulmonary stenosis and ventricular septal defect. *Bottom:* Atrial septal defect. Note the widely split second sound with both components preceding the O-point. Small "a" waves are recorded in both tracings. Systolic ejection murmur. Compare with Fig. 4.

the fourth sound, the tracing reveals a rapid rise, reaching a maximal peak at the moment of the closure of the atrioventricular valves. That component (from the end of the "a" wave to the peak of the systolic wave) appears to represent the isometric contraction.

The systolic wave has usually a "tent" shape, followed by a systolic depression which reaches at that level a plateau, and, finally, a sharp and rapid drop at the end of the systole. At that moment, the tracing reaches the base line, and this point marks the opening of the A-V valves and the beginning of the diastolic filling phase of the ventricles (O-point). The second sound precedes the beginning of the filling wave by 0.04 to 0.08 second (Fig. 1).

The early diastolic filling is represented in the ACG by a sharp rise which reaches a definite peak, this peak being coincident with a third sound. The duration of the RFW ranges from 0.04 to 0.12 second, depending on the total diastolic period of the cardiac cycle. This RFW represents, in height, 10 to 30% of the total amplitude of the tracing (100 per cent). From that point, the RFW is substituted by a slow rising which represents the slow filling wave. The slow filling wave ends at the level of the "a" wave and represents the end of passive diastolic filling (Fig. 1).

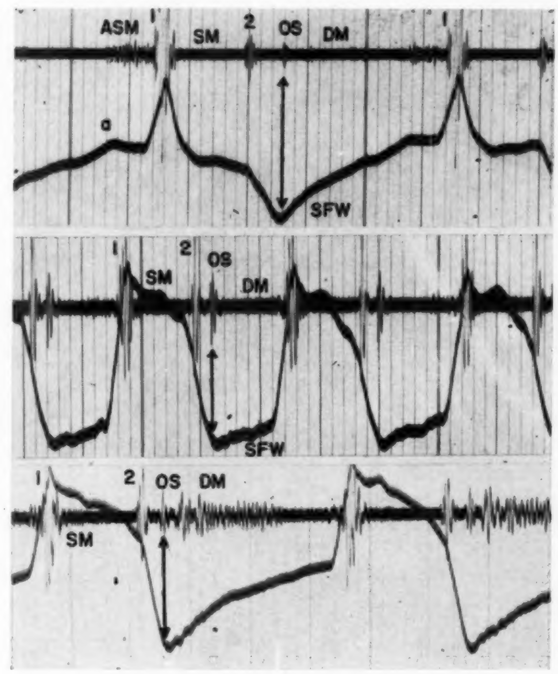

Fig. 4. Apexcardiogram of the left ventricle. Mitral stenosis. Note the opening snap of the mitral valve consistently coincident with the O-point. Observe also absence of rapid filling wave. Phonocardiographic signs of mitral stenosis. Mid-diastolic murmur starting after the beginning of SFW. In the top tracing, the opening snap could be confused with a third sound because of the long 2-OS interval (0.11 second). Compare with Fig. 11. The phonocardiograms were recorded at the apex.

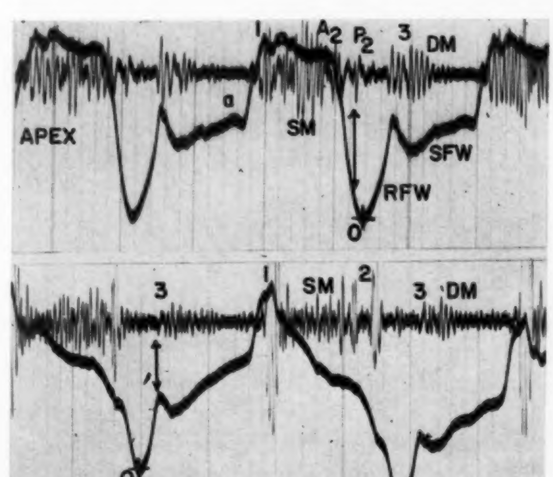

Fig. 5. Apexcardiogram of the left ventricle. Mitral regurgitation. Note the third sound and short diastolic murmur starting at the peak of the rapid filling wave, which is very prominent. In the top tracing, note the split of the second sound. The pulmonic component of the second sound should not be confused with the opening snap since it occurs before the O-point. Compare with Fig. 4.

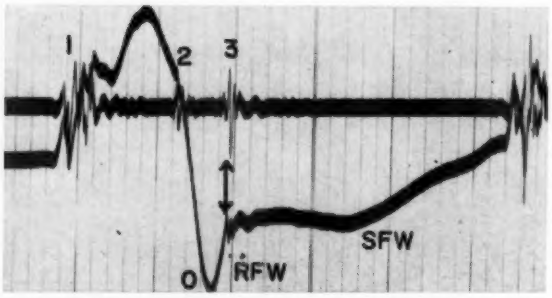

Fig. *6*. Apexcardiogram of the right ventricle. Constrictive pericarditis. Note a prominent third sound coincident with the peak of rapid filling wave.

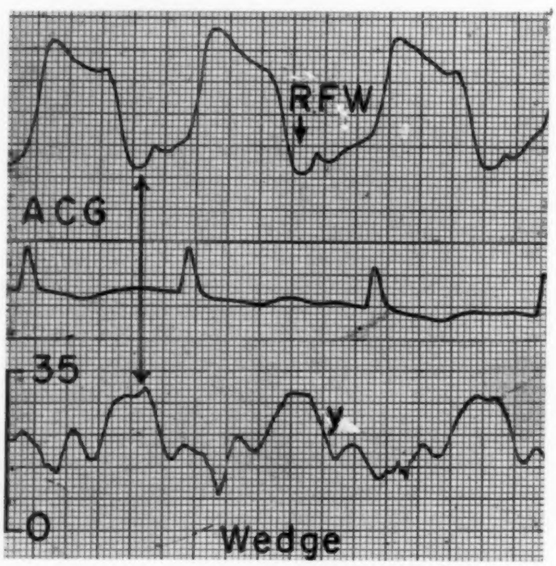

Fig. *7*. Simultaneous recording of the left ventricular apexcardiogram, electrocardiogram, and pulmonary wedge tracings in a patient with mitral regurgitation. Note the beginning of RFW (O-point) coincident with the peak of the "v" wave (opening of the mitral valve).

Time relationship of the events in the cardiac cycle as related to the apexcardiogram

1. First sound. The first sound usually precedes the peak of the systolic wave by an average of 0.02 second. In conditions associated with splitting of the first sound, both components should precede the peak of the systolic wave. The ACG seems to be of important value in this particular instance, since it is possible to differentiate the split of the first sound from the systolic ejection click (Figs. 1 and 2). However, it should be mentioned that occasionally, due to very short isometric contraction as occurs in cases of severe right or left ventricular hypertension, the systolic ejection click will occur very early in systole and will be almost inscribed with the first sound, making the separation between the two components nearly impossible by any method.[1-3]

2. Systolic ejection click. The systolic ejection click follows the peak of the systolic wave by 0.04 to 0.08 second.[1,3] The differentiation from split first sound was discussed above (Fig. 2).

3. Mid-systolic click. The mid-systolic click usually coincides with the initial descending limb of the systolic wave and is often coincident with the systolic plateau.

4. Second sound. The ACG is of special value in differentiating the second sound from the opening snap.[7] However, it does not separate the two components of the second sound (A_2 and P_2), and in this particular instance the carotid tracing is a superior reference tracing. Nevertheless, both components of the second sound precede the beginning of the filling wave, and the differential diagnosis between opening snap and split second sound is based on this fact (Figs. 3 and 4).

5. Opening snap. The ACG is extremely useful in the identification of the opening

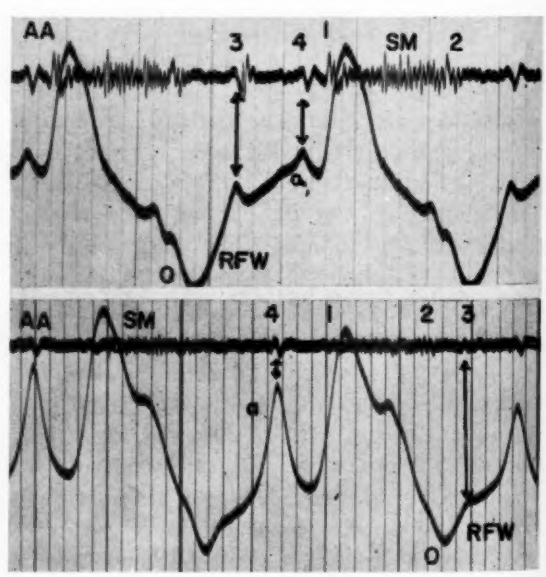

Fig. *8*. Apexcardiogram of the left ventricle. Two cases of aortic stenosis. Quadruple rhythm with third sound coincident with the peak of RFW and fourth sound with "a" wave. Note giant "a" wave in the bottom tracing, suggesting powerful left atrial contraction. Observe also that the ejection murmur starts after the peak of the systolic wave.

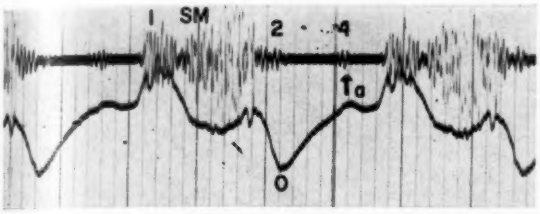

Fig. 9. Apexcardiogram of the right ventricle. Severe, isolated, pulmonary valvular stenosis. Systolic ejection murmur starting after the peak of the systolic wave. Note the fourth sound coincident with the peak of "a" wave in the apexcardiogram.

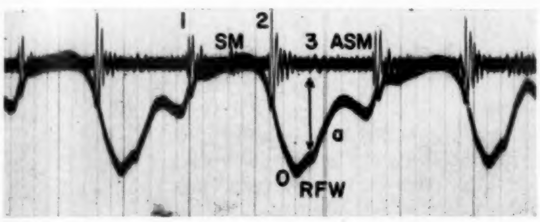

Fig. 10. Apexcardiogram of the left ventricle. Arteriosclerotic heart disease with left heart failure. Note fast heart rate (115 per minute), third sound gallop coincident with a rapid filling wave (*RFW*), and atrial systolic murmur (*ASM*) coincident with prominent "a" wave.

snap of the mitral or tricuspid valve. The opening snap should always be coincident with the beginning of the filling wave (O-point). Since the ACG records the movement of the chest wall overlying the ventricle, the time delay due to pulse wave transmission is negligible (Fig. 4).

6. *Third sound*. The third sound, when present, is coincident with the peak of the rapid filling wave which marks the end of rapid diastolic filling (Figs. 5 and 6). Simultaneous left ventricular ACG with pulmonary wedge or left atrial curves demonstrates that the beginning of the RFW (O-point) is coincident with the "y" descent of the "v" wave (which marks the opening of the A-V valve), and the end of the RFW is coincident with the end of the "y" descent, which marks the end of rapid emptying of the right or left atrium (Fig. 7).

7. *Fourth sound*. The ACG can be used to identify the fourth sound. The fourth sound, which is due to atrial contraction, produces an "a" wave in the ACG. Conditions associated with right or left auricular overload exaggerate the "a" wave of the ACG. The fourth sound should be coincident with the "a" wave of the ACG

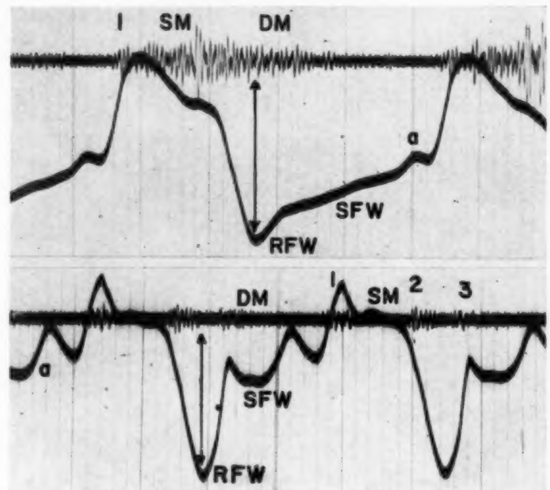

Fig. 11. Apexcardiogram of the left ventricle. *Top:* Patent ductus arteriosus without pulmonary hypertension. Note continuous murmur going through the second sound. The diastolic component of this murmur starts before the O-point in the ACG. *Bottom:* Aortic regurgitation. Observe the arterial diastolic murmur starting before the O-point, which is very prominent. Tall "a" waves. Compare with Fig. 4.

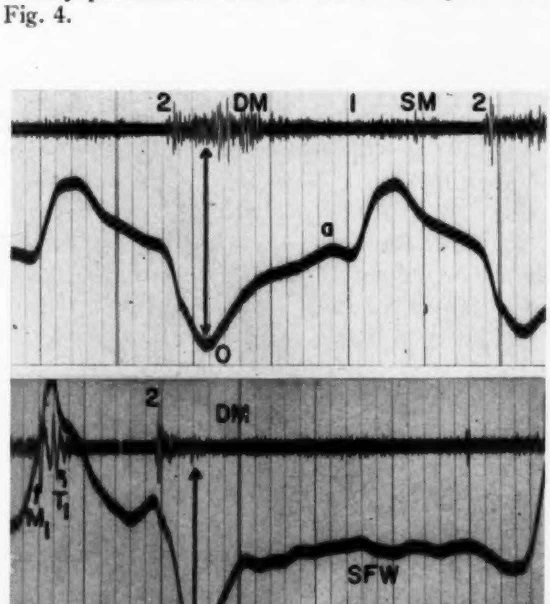

Fig. 12. Apexcardiogram of the right ventricle. *Top:* Moderately severe pulmonary regurgitation after pulmonary valvulotomy for correction of pulmonary stenosis. Note that the diastolic murmur precedes the O-point. *Bottom:* Pulmonary regurgitation in a patient with primary pulmonary hypertension (RV pressure of 130/5 mm. Hg). In addition to the diastolic murmur which starts before the O-point, note the split of the first sound, with both components preceding the peak of the systolic wave.

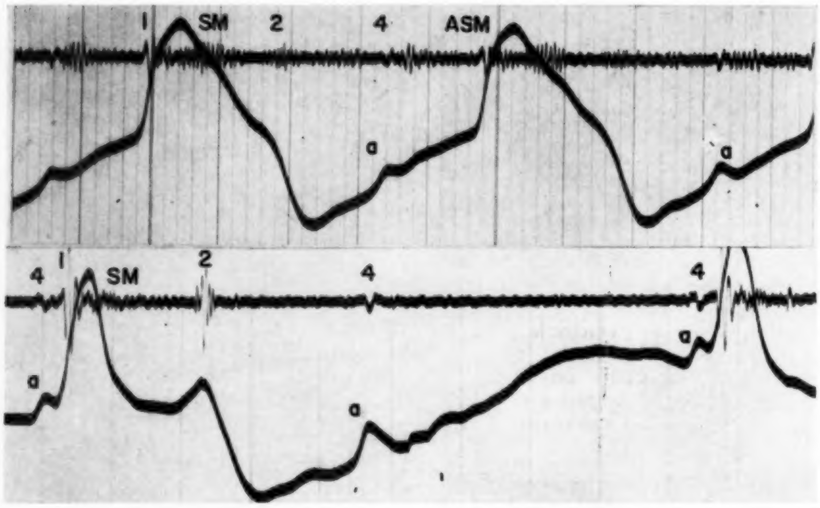

Fig. *13.* Apexcardiogram of the left ventricle. *Top:* Aortic stenosis and insufficiency with first-degree A-V block. Note the time interval between the atrial wave and the systolic wave (0.29 second). *Bottom:* Arteriosclerotic heart disease with 2:1 block. Note the "a" wave coincident with the fourth sound. These arrhythmias were confirmed by the electrocardiogram.

(Figs. 8 and 9). Simultaneous ACG with atrial curves demonstrates that atrial and apexcardiographic "a" waves occur simultaneously.

8. Systolic regurgitant murmurs. The ACG identifies a systolic regurgitant[10] murmur perhaps better than does the carotid tracing, in so far as time relationship is concerned. Mitral or tricuspid regurgitation and ventricular septal defects produce murmurs which start immediately after the first sound. When the heart murmur is recorded simultaneously with the ACG, it is noted that the murmur starts immediately after the peak of the systolic wave (Fig. 5).

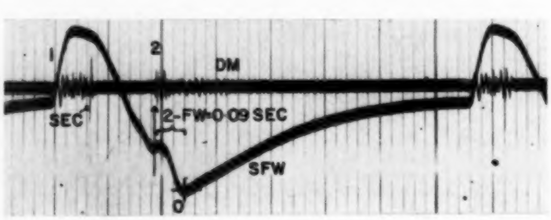

Fig. *14.* Apexcardiogram of the left ventricle. Mitral stenosis. Note the systolic ejection click occurring after the peak of the systolic wave. Observe the absence of the opening snap. Nevertheless, the distance between the second sound and the opening of the mitral valve can be calculated by measuring the time interval between the second sound and the beginning of the filling wave (*2-FW* interval). Note also the absence of a rapid filling wave.

9. Systolic ejection murmurs. Aortic stenosis, pulmonic stenosis, and murmurs due to increased flow across the pulmonic or aortic valves produce a typical murmur which starts somewhat late in systole and ends before the second sound. These murmurs, when timed against the ACG, start after the peak of the systolic wave, having maximal intensity during the first descending limb of the systolic wave, which represent the period of maximal ventricular ejection (flow at high velocity) (Figs. 3 and 9).

10. Atrial systolic murmurs. Mitral stenosis and tricuspid stenosis with sinus rhythm, septal defects, heart failure, etc., produce an atrial systolic murmur which starts with the "a" wave of the ACG and ends at the following isometric contraction, just prior to the peak of the systolic wave, as demonstrated in Figs. 4 and 10.

11. Atrioventricular diastolic murmur. The ACG is of special value in differentiating an atrioventricular murmur from an arterial diastolic murmur. In the former, the murmur starts at the beginning of the filling wave in the ACG, and in the latter, the murmur starts prior to the filling wave (Figs. 4 and 5).

12. Arterial diastolic murmurs. Aortic and pulmonary insufficiency produce a diastolic murmur that starts during iso-

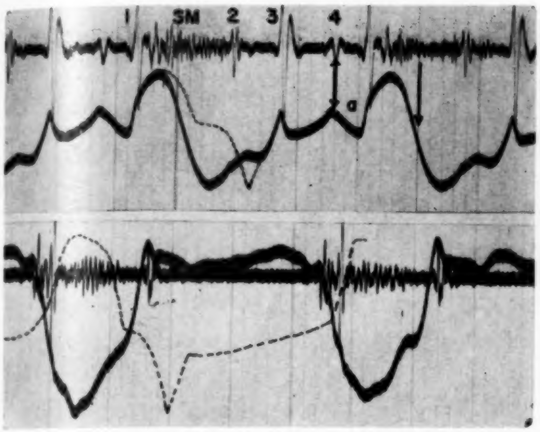

Fig. *15*. Artefacts in the apexcardiogram. *Top:* Somewhat common type of artefact. Note that there is a marked drop in the systolic wave (*arrow*), with a small positive wave at the level of the second sound. The late part of the rapid filling wave is well recorded and is coincident with the third sound. The "a" wave holds a normal relationship to the fourth sound. The expected configuration of the apexcardiogram is indicated by the dashed line. *Bottom:* Apexcardiogram of the right ventricle, demonstrating artefactual rapid filling wave. Note the systolic drop of the systolic wave. The two components of the second sound were identified in other tracings by the relationship to the dicrotic notch of the carotid tracing.

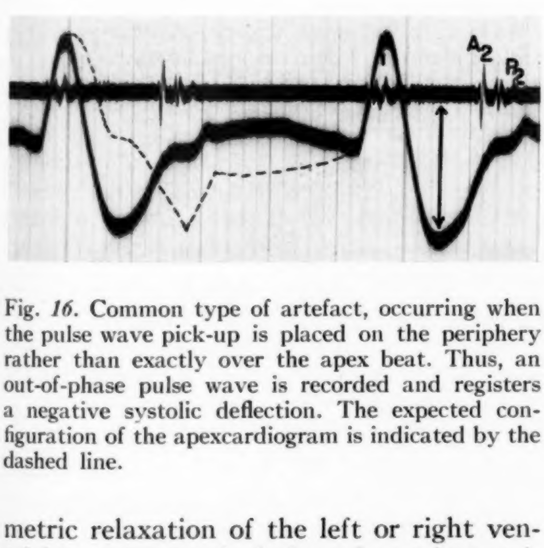

Fig. *16*. Common type of artefact, occurring when the pulse wave pick-up is placed on the periphery rather than exactly over the apex beat. Thus, an out-of-phase pulse wave is recorded and registers a negative systolic deflection. The expected configuration of the apexcardiogram is indicated by the dashed line.

metric relaxation of the left or right ventricle, consequently before the atrioventricular valves open (Figs. 11 and 12). In that circumstance, the ACG readily identifies the type of murmur by its relationship to the diastolic filling wave as described above.

13. Arrhythmias. The apexcardiogram seems to be a useful aid in the identification of certain types of arrhythmias and atrioventricular conduction effects. As demonstrated in Fig. 13, a first-degree A-V block is readily identified by prolongation of the interval between the "a" wave and the beginning of the systolic wave.

Right ventricular apexcardiogram. By means of this technique, the right ventricular ACG was very seldom recorded in a normal subject. In a few cases in which tracings were obtained at the left sternal border, third to fifth intercostal space, no reproducibility was obtained. Perhaps a more sensitive type of device requiring a more complex type of equipment, as described by Eddleman[11,12] and Harrison,[13] would allow a more nearly accurate tracing. However, in conditions associated with right ventricular overload, a right ventricular ACG can be recorded and presents the same components as described above for the ACG of the left ventricle (Figs. 2, 3, 6, 9, and 12). Occasionally, as was emphasized by Hartman,[8] one may be able to record an ACG from the right and left ventricles in the same patient.

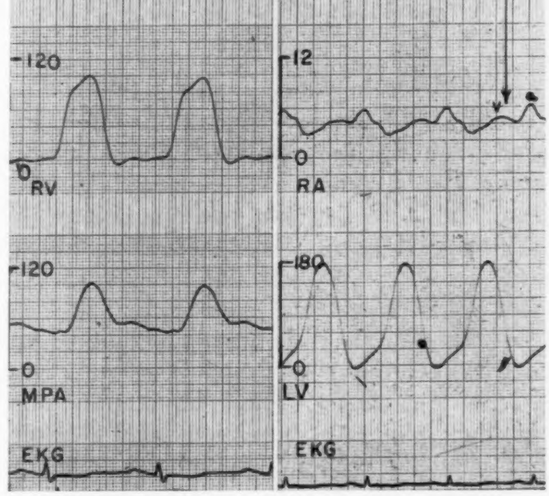

Fig. *17*. Simultaneous right ventricular apexcardiogram with electrocardiogram and pressure curves of the right ventricle (*RV*), main pulmonary artery (*MPA*), right atrium (*RA*), and left ventricle (*LV*). Note "a" wave of the ACG coincident with "a" waves in the right atrial curves and P waves in the EKG. Observe also the beginning of ejection in the MPA curves coincident with the peak of the systolic wave in the ACG.

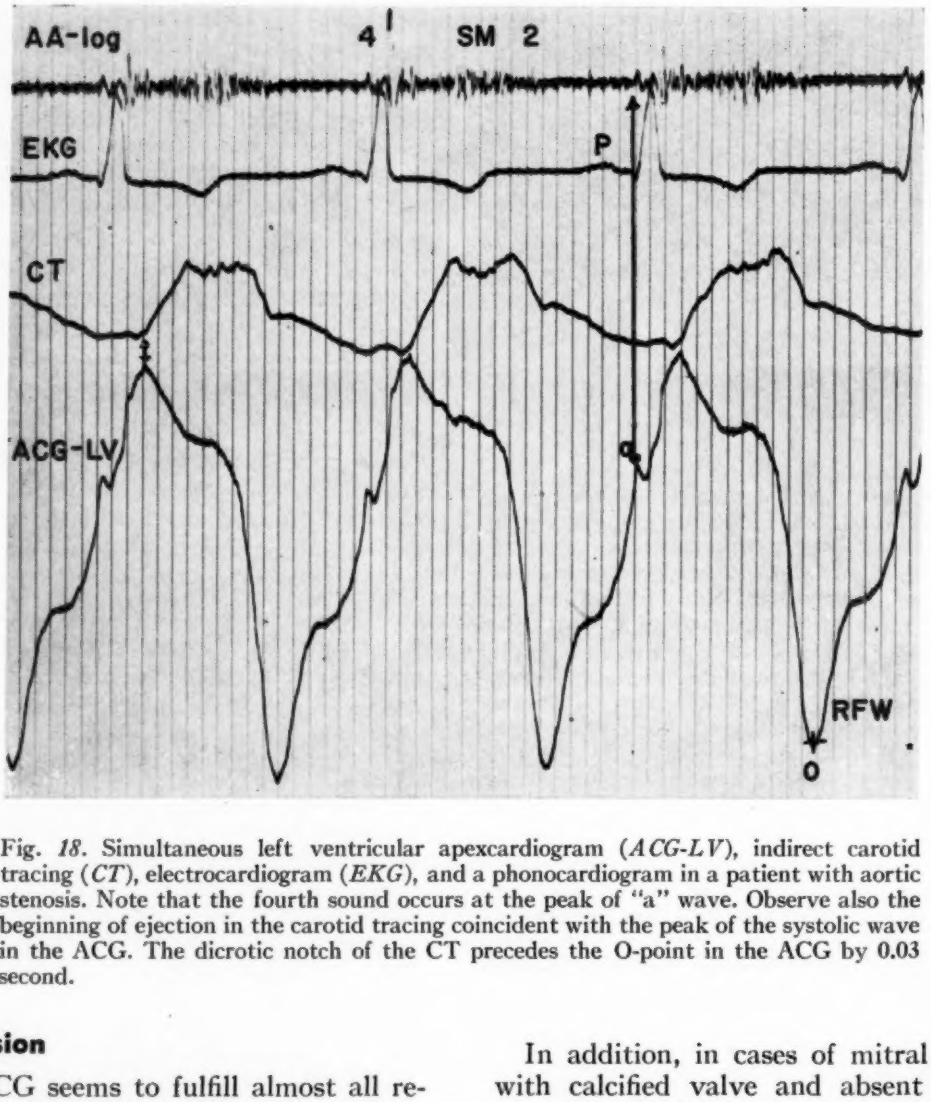

Fig. *18*. Simultaneous left ventricular apexcardiogram (*ACG-LV*), indirect carotid tracing (*CT*), electrocardiogram (*EKG*), and a phonocardiogram in a patient with aortic stenosis. Note that the fourth sound occurs at the peak of "a" wave. Observe also the beginning of ejection in the carotid tracing coincident with the peak of the systolic wave in the ACG. The dicrotic notch of the CT precedes the O-point in the ACG by 0.03 second.

Discussion

The ACG seems to fulfill almost all requirements of an ideal reference tracing in phonocardiography. It does not provide information about the two components of the second sound, although it differentiates the second sound from the opening snap of the mitral valve, as demonstrated in Figs. 3, 4, and 5. It is, by far, superior to the carotid tracing, electrocardiogram, and, in many instances, it does obviate the need to have a multichannel sound recorder for time purposes. In that fashion, an ordinary two-channel phonocardiograph can be used with great accuracy. Perhaps its greatest value lies in the identification of the diastolic events of the cardiac cycle, and particularly in the differential diagnosis between the second sound, the opening snap, and the third sound, which differentiation provides for the most common mistakes made in phonocardiography.

In addition, in cases of mitral stenosis with calcified valve and absent opening snap it is possible to measure the distance between the second sound and the beginning of the filling wave (2-FW), and this interval has exactly the same value as 2-OS interval (Fig. 14). This fact should be strongly emphasized because of its practical usefulness.

Aside from its value as a reference tracing, the ACG can show interesting abnormalities of its components in the case of some valvular lesions or cardiac defects. As we have demonstrated in a previous report,[7] the analysis of the diastolic component of the ACG seems to be helpful in the differential diagnosis between mitral stenosis and regurgitation. In mitral stenosis, the rapid filling wave is absent (Fig. 4), and in mitral regurgitation, there is an accentuation of this component (Fig. 5). In the presence of combined re-

gurgitation and stenosis, the ACG seems to be of special value. In this circumstance, the ACG continues to show absence of RFW when stenosis predominates, and presence of RFW when regurgitation is the primary lesion. Conditions associated with ventricular diastolic overloading, as in aortic and pulmonic insufficiency, septal defects, etc., tend to increase the rapid filling wave of the ACG. On the other hand, conditions associated with ventricular systolic overload, as in aortic and pulmonic stenosis, systemic and pulmonic hypertension, etc., tend to increase the amplitude of the "a" wave, and changes in the shape of the systolic wave are observed as well, as demonstrated in Figs. 8 and 9. However, the abnormalities of the systolic component of the ACG have been variable, and a special study is being presently undertaken in order to clarify some of these problems.

The technique of recording the ACG must be developed by practice, and initial attempts usually result in artificial curves, as demonstrated in Figs. 15 and 16. Difficulty in recording the apexcardiogram is usually encountered in patients with pulmonary emphysema, marked chest deformity, and obesity. We do not wish to convey an impression of overenthusiasm for the value of the method described or to imply that the recording of displacement curves or attempts to explain their possible values is a new concept. Others[8,15-18] have tried to define a physiologic role for the components of the apexcardiogram, but very few have attempted correlation with intracardiac pressure curves.[14] We believe that at the present time we have accumulated enough material to confirm that the components of the ACG represent the mechanical events of the left and right ventricles (Figs. 17 and 18).

Summary and conclusion

The value of the apexcardiogram as a reference tracing in phonocardiography has been emphasized. The greatest value of the apexcardiogram (ACG) seems to be in the identification of the diastolic events of the cardiac cycle, since no reference tracing presently in use can provide this information.

The abnormalities of the ACG in conditions associated with ventricular systolic or diastolic overloading were discussed. The great usefulness of the ACG in cases of mitral valve disease was emphasized.

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Cardiopulmonary changes in scleroderma
A physiologic study

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Scleroderma is a generalized connective-tissue disorder of unknown etiology which frequently produces cardiopulmonary damage. The disease occurs mainly in women between the third and the sixth decades, and evidence of visceral involvement usually follows the articular and cutaneous manifestations.[1,2] Occasionally, pulmonary or cardiac symptoms may herald the onset of the disease,[1,3] but in such cases the diagnosis is usually missed.

The general clinical picture of scleroderma is well known, but the hemodynamic and pulmonary derangements it may produce have received insufficient emphasis. For this reason, detailed cardiopulmonary studies were done in 4 patients with scleroderma heart disease in the hope of characterizing the derangements more precisely. Ventilatory and diffusion studies and right heart catheterization were performed in each instance. The clinical diagnosis in the 4 patients was based mainly on the involvement of the skin and various organs, including the esophagus, and on skin biopsies. There was no evidence of valvular, hypertensive, or overt coronary arterial disease.

Case Material

Case 1. A 40-year-old Negro woman first noted Raynaud's phenomenon in early 1958. Progressively, the skin over the arms, chest, and legs became tight and shiny, with some limitation of motion of the joints. In July, 1958, she underwent a right thoracotomy after a gunshot wound. The postoperative course was complicated by a reaction to transfusion which was characterized by chills and fever and a residual pleural thickening. Blood serology was positive. Repeated lupus erythematosus cell preparations, latex fixation, and sheep cell agglutination tests were negative. Sedimentation rate was 65 mm. per hour. The electrocardiogram was normal. Fluoroscopy with barium swallow showed a dilated, inert esophagus. Skin biopsy was negative.

In July, 1959, dysphagia, heartburn, exertional dyspnea, orthopnea, frequent bouts of paroxysmal nocturnal dyspnea, and dependent edema made their appearance. She denied cough, pleurisy, loss of weight, or hemoptysis. The skin had become waxy, shiny, atrophic, and bound down over the dorsum of fingers, hands, and wrists. There were similar changes over the thorax and face, causing restriction of temporomandibular motion. No lymphadenopathy or alopecia was noted. The tongue was normal. The lungs were clear except for dullness and decreased breath sounds at the right base. Blood pressure was 120/70 mm. Hg. The heart was not enlarged, and no murmurs were heard. The second sound at the base in the pulmonic area was split. The liver was not enlarged, but the tip of the spleen was felt. The rest of the physical examination was noncontributory.

The hemoglobin was 13 Gm. per 100 ml. Urinalysis was normal. Blood urea nitrogen and serum electrolytes were normal. Albumin/globulin ratio was 3.6/4.8 Gm.; Bromsulphalein test showed 16 per cent retention after 45 minutes. The other liver function tests were normal.

X-ray studies showed slight cardiomegaly and blunting of the right costophrenic angle (Fig. 1). The wrists and hands were normal. Barium swallow illustrated rigidity of the distal esophagus, creating a degree of functional obstruction. Barium remained

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in the esophagus at least 1 hour. Ventilatory and cardiac catheterization studies are presented in Tables I and II.

Over a 4-week period she received 73 Gm. of versene (sodium EDTA), with dramatic improvement in the skin and motion of the joints. Three months later, the results of vitalometry and right heart catheterization were unchanged. On follow-ups, progressive changes in the skin have been observed.

Case 2. A 52-year-old white man first noted stiffness and thickening of the skin over the hands and feet sufficient to restrict motion of the joints in August, 1958. He experienced no pain or swelling of the joints. When seen 2 months later, he denied dysphagia and cardiorespiratory symptoms. The skin over the extremities was thickened and bound down, limiting motion in the fingers, wrists, and feet. There was definite weakness of the muscles of the hands, biceps, triceps, and quadriceps bilaterally. Examination of the heart and lungs was within normal limits.

The hemoglobin level was 11.3 Gm.; total and differential leukocyte counts were normal. Urinalysis was negative. Serology, lupus erythematous cell preparation, latex fixation, and sheep cell agglutination were negative. Serum electrolytes were normal. Albumin/globulin ratio was 4.0/2.8 Gm. Ventilation studies were normal. X-rays of the chest were normal. The electrocardiogram revealed nonspecific T-wave changes, which disappeared at a later date. A barium swallow demonstrated only a small hiatus hernia. Films of the hands were negative. Skin biopsy was compatible with scleroderma.

He was treated with relaxin (40 mg. a day) over a 3-week period, with prominent subjective but no objective improvement. In February, 1959, he was given a 3-week course of versene, during which time there was subjective improvement in the skin and motion of the joints; however, repeated measurement of the vital capacity showed no change.

He was readmitted in January, 1960, with progressive tightening of the skin. He again denied cardiorespiratory symptoms, and physical examination of the heart and lungs was normal. He was again given 45 Gm. of versene, without definite objective changes. Prior to the above therapy, right heart catheterization and ventilation studies were performed (Tables I and II).

Case 3. A 52-year-old Negro woman had noted progressive tightening of the skin over the dorsum of the fingers and hands for 10 years, and inability to make a fist or to open her mouth widely for 2 years. She experienced pain and discoloration of the finger tips on exposure to cold. She also complained of frequent heartburn, sensation of food stopping in the chest, and progressive exertional dyspnea for 4 months. She sometimes experienced nocturnal coughing paroxysms, allegedly productive of frothy sputum which contained streaks of blood. She specifically denied orthopnea, peripheral edema, fever, pleuritic pain, and loss of weight.

Physical examination revealed a chronically ill woman with normal vital signs. She was able to lie flat without distress. There was generalized lymphadenopathy. There was depigmentation over the malar areas and tautness of the skin over the face. The tongue appeared to be normal. The lungs were clear. The heart was diffusely enlarged, and there was pulsation in the left parasternal region. Normal sinus rhythm was present, and a soft systolic murmur was heard over the precordium. The second heart sound in the pulmonic area was split, and its second component was accentuated. Examination of the abdomen was negative. The skin over the forearms and fingers was taut, fixed, and shiny. There were punctate scars on several of

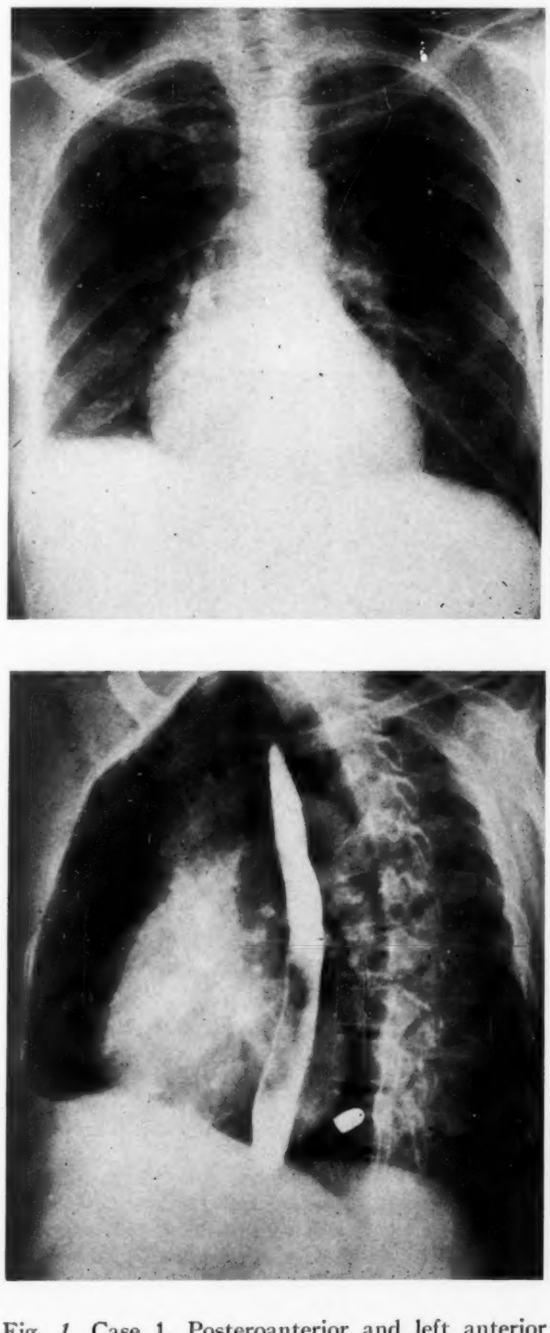
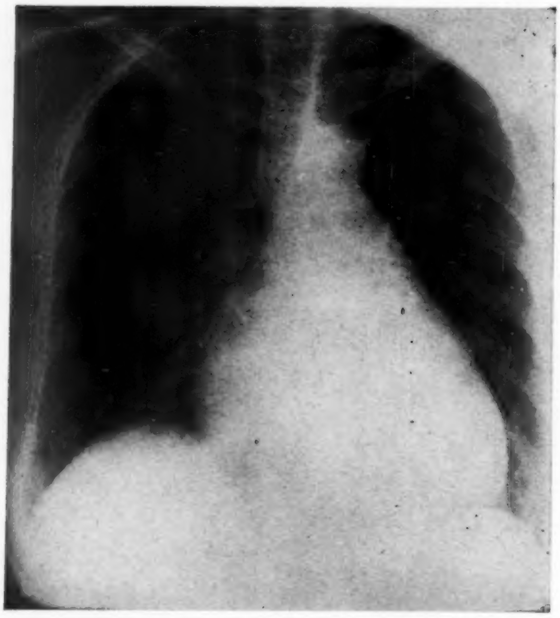


Fig. *1.* Case 1. Posteroanterior and left anterior oblique views of the chest. A bullet is seen in the left lower lung field just lateral to the thoracic vertebra.



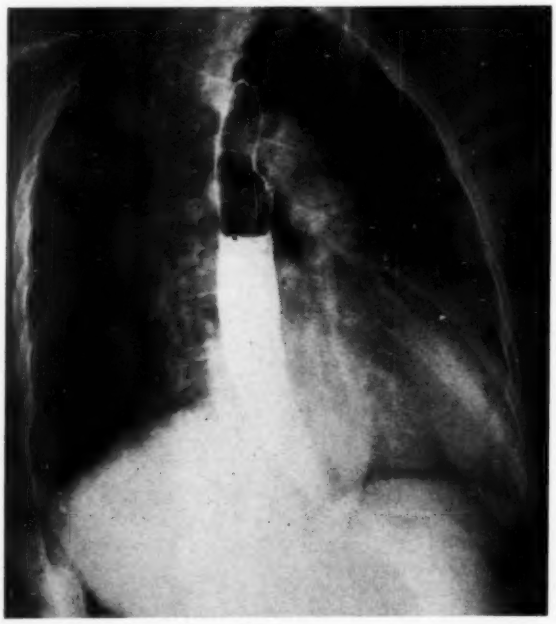


Fig. *2*. Case 3. Posteroanterior and right anterior oblique views of the chest.

the finger tips. There was no cyanosis, clubbing of the fingers, or edema.

Hemogram and urinalysis were normal. Blood serology was positive. Lupus erythematosus cell preparation, sheep cell agglutination, and latex fixation tests were negative. Blood urea nitrogen and serum electrolytes were normal. Albumin/globulin ratio was 3.8/3.5 Gm., and a Bromsulphalein test showed 13 per cent retention after 45 minutes. Thymol turbidity was 9 units.

The electrocardiogram showed right axis deviation and right ventricular preponderance. Skin biopsy was reported as compatible with scleroderma. Cardiac fluoroscopy disclosed diffuse cardiomegaly. The pulmonary artery segment was prominent (Fig. 2). The esophagus was dilated and atonic. Ventilatory studies demonstrated marked restrictive-obstructive defect (Table I), and right heart catheterization showed moderate pulmonary hypertension and decreased cardiac output (Table II).

Case 4. A 45-year-old Negro woman was first seen in 1957, complaining of pain and stiffness of the fingers, wrists, and ankles, profound weakness, dysphagia, fever and 50-pound loss of weight during the preceding year. She was totally immobilized by the complaints. The skin of the extremities and face was tight and atrophic. A skin-muscle biopsy showed changes that were compatible with scleroderma. The patient also had amicrocytic hypochromic anemia, but total and differential leukocyte counts were normal. Lupus erythematosus cell preparation was negative. Sheep cell agglutination and serology were positive. Albumin/globulin ratio was 2.7/3.8 Gm. X-ray studies of the lungs and heart were normal, but the upper two thirds of the barium-filled esophagus was dilated and atonic.

Her general condition improved on steroid therapy (Meticorten, 10 to 20 mg. per day), and after several weeks she was able to walk without assistance. Subsequent examinations revealed gradual increase of intensity of the second heart sound in the pulmonic area. A chest film taken in May, 1959, showed diffuse cardiomegaly for the first time, but she had no symptoms referable to the heart. In June, 1959, she experienced a single episode of hemoptysis, unassociated with chest pain or cough, and the lung fields were clear radiographically. The electrocardiogram showed right axis deviation, right ventricular preponderance, and tall peaked P waves (P pulmonale). The heart remained enlarged clinically, and the accentuated and split pulmonic second sound was noted to be fixed throughout the respiratory cycle. Data obtained by right heart catheterization are presented in Table II. Ventilatory studies, demonstrating restrictive defect of severe degree, are given in Table I.

Discussion

The frequency of cardiac involvement in patients with scleroderma is unknown, but at postmortem, evidence of myocardial involvement was found by Piper and Helwig[3] in 28 of 31 cases. Cardiac manifestations are attributable either to direct involvement of left ventricular muscle or to pulmonary fibrosis. In patients with fibrotic myocardial changes, left ventricular failure may occur; in those with pulmonary fibrosis, right ventricular failure is the end result. A diffusely enlarged and a weakly pulsating left ventricle is a late manifestation of the disease and simulates, in some respects, pericardial effusion.[4-6]

Eighteen months after the appearance

Table I. Vitalometric studies in patients with scleroderma

	Case					Normal
	1,a	*1,b*	*2*	*3*	*4*	
Forced vital capacity (FVC)	2.2	2.2	3.63	1.6	1.7	
$\frac{\text{FVC}}{\text{Predicted FVC}} \cdot 100$	53	55	83	50	44	100 ± 11
$FEV_{0.5}$	1.5	1.4	2.6	0.7	1.2	
$\% \frac{FEV_{0.5}}{FVC}$	68	64	72	44	71	67.8 ± 5.8

$FEV_{0.5}$: Forced expiratory volume, 0.5 second

Table II. Hemodynamic findings in patients with scleroderma

Case	*Pulmonary arterial pressure (mm. Hg)*		*Right auricular mean pressure (mm. Hg)*	*Pulmonary wedge mean pressure (mm. Hg)*	*Brachial artery*	
	S/D	*Mean*			*Content (vol. %)*	*Saturation (%)*
1,a	28/10	(17)	3	6	15.44	94
1,b	26/12	(19)	3	7	13.16	92
2.	14/4	(9)	0	2	17.54	91
3.	64/30	(40)	3	5	17.92	94
4.	71/31	(51)	4	–	13.05	89

Case	*Cardiac output (L./min.)*	*Cardiac index (L./min./M.²)*	*Breathing 100% oxygen*			
			Arterial pCO_2 (mm. Hg)	*Arterial pO_2 (mm. Hg)*	*A-a PO_2 gradient (mm. Hg)*	*"Shunt" (%)*
1,a	3.57	1.96	35	273	379	20.2
1,b	6.10	3.45	40	365	297	17.7
2.	2.53	1.59	32	233	431	19.4
3.	1.57	0.90	—*	194	455	18.7
4.	2.41	1.53	46	370	287	11.7

*Assumed to be 40 mm. Hg.
S: Systolic. D: Diastolic.

of changes in the skin the patient of Case 1 gradually developed cardiomegaly and congestive failure. Her cardiac output was quite low. As was anticipated, treatment with versene resulted in marked clinical improvement[7]; somewhat unexpectedly, her cardiac output became normal (Table II). It is not clear whether the improvement in cardiac output was the result of versene therapy alone or of the combined effect of versene and digitalis therapy. In actual fact, it seems doubtful that either drug would greatly improve the cardiac status if diffuse fibrosis were present in the left ventricular muscle. Also, in Case 2, there was a reduced resting cardiac output, but there was no clinical evidence of cardiac disease, suggesting perhaps that myocardial

involvement may occur before clinical symptoms appear. The electrocardiogram in this patient showed abnormal T waves in the course of his illness, changes usually thought to be consistent with diffuse myocardial damage.

In Cases 3 and 4, electrocardiographic evidences of right ventricular overload were present, and marked pulmonary hypertension was found by cardiac catheterization (Table II). In these cases, it is believed that the disease process was primarily concentrated in the lungs. Such involvement has been reported in up to 50 per cent of patients with the disease.[3,8-10] However, a higher incidence would undoubtedly be found if pulmonary function tests were routinely performed in such patients. Alterations in pulmonary function are dependent upon the location and the extent of the fibrotic process. Involvement of the skin, the muscles of the thorax, the pulmonary parenchyma, and the pleura interferes with respiratory excursion and produces a restrictive type of ventilatory defect. In this instance, the total vital capacity is reduced. This was observed in all of our cases, but to a lesser extent in Case 2. In instances in which the fibrotic process involves the bronchial musculature, leading to emphysema and bronchiectasis,[11] an obstructive type of defect may become apparent. Evidence of such a defect was obtained in Case 3 (Table I). A combined type of defect (restrictive and obstructive) may be present, therefore, in certain patients with this disease. Versene therapy in Case 1 resulted in no objective improvement in pulmonary ventilation, although clinically the subject felt better. In both instances (Cases 1 and 4) in which diffusion studies by the single-breath carbon-monoxide technique were performed, a marked reduction in diffusion was observed. The diffusion capacities were 11 and 17 ml. CO/min./mm.Hg, respectively, as compared to a normal value of 30 ml.CO/min./mm. Hg. In Case 4 the low diffusion capacity could partly be explained by the low hemoglobin (6.5 Gm. per 100 ml.) present at the time of this study.

Breathing 100 per cent oxygen for 30 minutes resulted in a large alveolar-arterial (A-a) oxygen tension gradient in all of our cases (Table II). This gradient ranged between 287 and 455 mm. Hg, indicative of venoarterial shunting* through the lungs. The magnitude of the shunts varied between 11.7 and 20.2 per cent of the respective cardiac output. In Case 1 the shunt did not significantly decrease after versene therapy which was accompanied by clinical improvement.

The large alveolar-arterial (A-a) oxygen tension gradient observed in patients with scleroderma has been thought to represent an alveolar-capillary block, a diffusion defect, caused by thickening of the alveolar septa.[14] But in at least 2 of our patients (Cases 1 and 4) the A-a gradient resulted from a composite of two physiologic defects: a diffusion defect, as demonstrated by the reduction in diffusion capacity of carbon monoxide, and an intrapulmonary venoarterial shunting, both of which may have arisen from the same anatomic lesion, resulting in perfused nonventilated units of lung tissue.

It is apparent, therefore, that in our cases of scleroderma the disease process involved both the heart and the lungs, with one organ predominating in its clinical manifestations. In instances in which the heart is primarily affected the fibrotic process in the ventricular muscles results in a reduction in the cardiac output (Cases 1 and 2) prior to the clinical manifestations of left heart failure. But when the lungs are predominantly involved, pulmonary hypertension and the clinical picture of cor pulmonale appear. However, the findings in our patients suggest that in scleroderma an intrapulmonary venoarterial shunting and a diffusion defect are usually present, even in instances in which the heart appears to be the organ mostly involved.

Summary

Four patients with scleroderma were studied by means of cardiac catheterization and measurements of pulmonary function.

*The degree of pulmonary venoarterial shunting is calculated from the following equation[12]:

$$\%\ \text{Shunt} = 100 \left(1 - \frac{\Delta\text{A-V}_{O_2}\ \text{difference}}{\Delta\text{A-V}_{O_2}\ \text{difference} + G} \right)$$

where G represents the alveolar-arterial oxygen tension gradient multiplied by the Sendroy factor. This latter factor is equal to 0.003. The alveolar oxygen tension (PA_{O_2}) was calculated from the alveolar equation.[13] The arterial oxygen tension (Pa_{O_2}) was determined polarographically.

In one case the studies were repeated after versene therapy and subjective clinical improvement. In 2 cases, a single-breath carbon-monoxide test was performed.

In 2 cases, marked pulmonary hypertension was found, and in all 4 cases, reduction in the cardiac output and index was demonstrated.

All patients exhibited evidence of restrictive ventilatory disturbance, but only one showed evidence of an obstructive type of pulmonary ventilatory defect. All patients exhibited a large intrapulmonary venoarterial shunt. In the 2 patients in whom the single-breath carbon-monoxide technique was performed a diffusion defect was also observed. The large A-a PO_2 gradient described in these patients when they were breathing room air was the result of the combination of a diffusion defect and pulmonary venoarterial shunts.

Versene therapy resulted in marked subjective improvement, but failed to improve the pulmonary ventilation or to diminish the intrapulmonary shunt.

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Experimental and laboratory reports

The effects of infusing quinidine sulfate and potassium chloride, separately and combined, on conduction times of the dog heart

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The production of conduction defects by high levels of quinidine, both within the atrium[1] and within the ventricle,[2] is well recognized. Likewise, it is well recognized that disappearance of P waves as well as slowing of conduction, both atrioventricular and intraventricular, occur in the presence of hyperkalemia.[3,4] The question arises whether the simultaneous presence of high levels of quinidine and hyperkalemia would be additive or synergistic, with respect to the production of conduction defects. In an effort to answer this question, we have carried out experiments in which potassium chloride and quinidine sulfate, separately and in combination, were infused into normal dogs. Plasma levels of both potassium and quinidine were determined, and electrocardiographic tracings were obtained for analysis of conduction times.

Method

Nineteen mongrel dogs which weighed from 5.2 to 17.5 kilograms were used. All experiments were carried out under sodium pentobarbital anesthesia, and blood pressure was monitored continuously in all animals by use of a damped mercury manometer. Serial electrocardiographic tracings were taken on each animal by means of a Sanborn Visocardiette and standard limb leads. Potassium chloride as an isotonic solution was infused intravenously at rates which varied from 1 to 4 c.c. per minute; the rates were determined by the size of the dogs and by their responses. Quinidine sulfate was dissolved in mammalian Ringer-Locke's solution and likewise was given by intravenous infusion. When both potassium chloride and quinidine sulfate were administered, the quinidine sulfate was dissolved in the potassium chloride solution. Blood for analysis was withdrawn from the femoral vein. Serum potassium was determined by use of a Perkin-Elmer Model 52A flame photometer, with lithium used as an internal standard. Quinidine was determined by means of the fluorometric method of Brodie,[5] after deproteinization by metaphosphoric acid.

In some experiments, potassium chloride alone was infused (8 cases). In others, quinidine sulfate alone was infused (5 cases). High levels of quinidine and potassium together were achieved in three different ways: (a) by infusing both substances together from the beginning of the experiment (3 cases); (b) by first elevating the plasma potassium and then superimposing

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infusions of quinidine (3 cases); (c) by first elevating the plasma quinidine and then superimposing infusions of potassium chloride (3 cases). Since no differences in results from these three procedures were apparent, they are considered together in the presentation of data.

Results

Effects upon cardiac rate and rhythm. When potassium chloride alone was given, no consistent changes in cardiac rate were produced until P waves disappeared, partial A-V block was produced, and/or ectopic beats occurred. No changes in blood pressure were observed until some change in cardiac rhythm took place. As the plasma quinidine was progressively elevated, the cardiac rate progressively slowed and the blood pressure progressively fell. In all but one animal, by the time the level of quinidine in the blood reached 9 or 10 mg. per liter, the heart rate was between 50 and 70. This should be compared with the initial sinus tachycardia of 140 to 160 beats per minute which was found in these animals, as it is found in most dogs under sodium pentobarbital anesthesia. When quinidine alone was given, no rhythm other than a normal sinus rhythm was ever seen. When potassium and quinidine were both given, no additive effect of the hyperkalemia upon the quinidine-induced slowing of a sinus rhythm was observed.

Effects upon the P waves. In conformity with findings previously reported,[3,4] P waves disappeared in dogs into which potassium chloride alone was infused, when the plasma potassium was sufficiently elevated. The levels of plasma potassium at which the P waves disappeared in these animals varied from 6.2 to 8.7 mEq. per liter (Fig. 1). When levels of potassium of 7 mEq. per liter and above were achieved and the P waves persisted, some widening of the P waves occurred. When quinidine alone was infused, slight, but definite and progressive, widening of the P waves was observed. The quantitative data bearing upon the point are presented in Fig. 2 and show that the P-wave duration is approximately doubled with levels of plasma quinidine of 10 mg. per liter. When both potassium and quinidine were infused, in 8 instances it was possible to determine P-wave

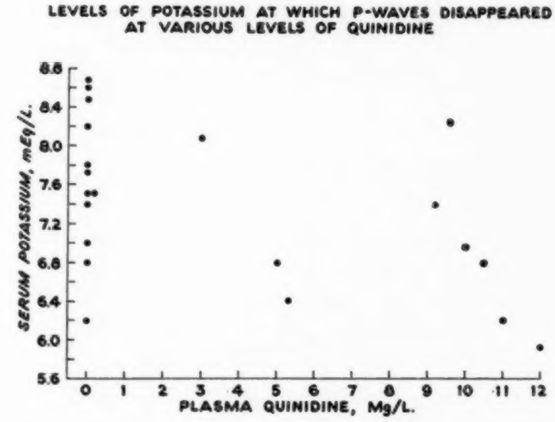

Fig. *1*. The levels of serum potassium at which P waves disappeared when no quinidine was infused are indicated by those points appearing vertically over zero concentration on the x-axis. The other points show the concentration of *both* potassium and quinidine when P waves disappeared.

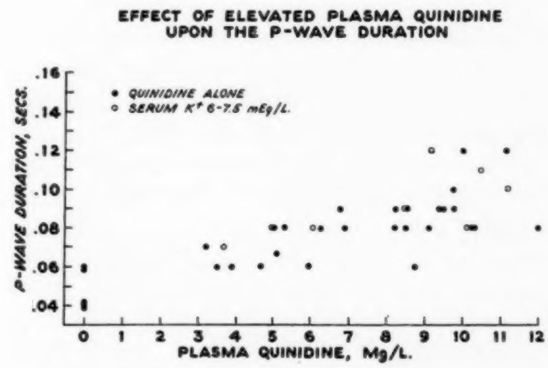

Fig. *2*. No data from animals with serum potassium above 7.5 mEq. per liter are shown, because P waves did not persist at levels of serum potassium higher than this when quinidine was given. No data for animals with serum potassium below 6 mEq. per liter are given, because such levels could scarcely be called hyperkalemic.

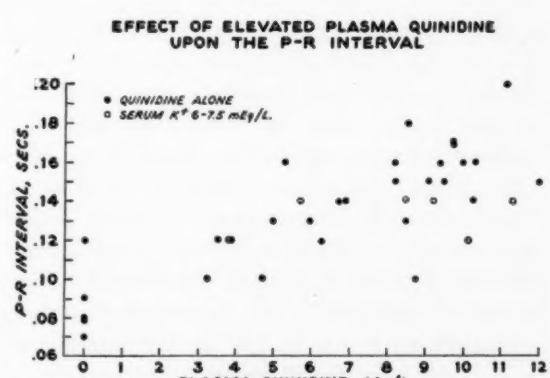

Fig. *3*. The comments made relative to Fig. 2 also apply here.

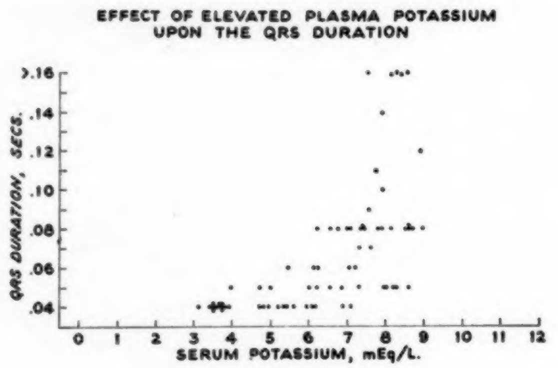

Fig. *4*. The QRS duration was read to the nearest 0.01 second. This accounts for the grouping of QRS times as seen in Figs. 4 and 5.

duration in animals with levels of plasma potassium above 6 mEq. per liter. These data are shown in Fig. 2 and demonstrate that hyperkalemia of this degree does not alter quinidine slowing of atrial conduction. The combination of high levels of quinidine in the blood and hyperkalemia did not alter the effective concentration of plasma potassium which produced disappearance of P waves. The data which establish this point are shown in Fig. 1. Although it may appear that when the plasma quinidine is elevated, the mean level of potassium necessary to produce disappearance of P waves is lowered, analysis of the data by the nonparametric Mann-Whitney U test shows that the trend is not significant even at the .05 level.

Effects upon A-V conduction time. With infusion of potassium chloride alone, both disappearance of P waves and 2:1 and higher degrees of A-V block were produced. With infusion of quinidine alone, there was progressive prolongation of the A-V conduction time (measured by the P-R interval) as the level of plasma quinidine was elevated; the P-R interval was approximately twice that of the controls with levels of plasma quinidine above 8 mg. per liter. These data are presented in Fig. 3. There were 6 experiments in which levels of plasma potassium of 6.0 to 7.5 mEq. per liter were produced with simultaneous infusion of quinidine, and in which P waves persisted without 2:1 or higher degrees of A-V block; in all of these, prolongation of the P-R interval was not greater than that seen with quinidine alone. These data are likewise shown in Fig. 3. Thus, these experiments indicate that the effect of hyperkalemia and quinidine upon the A-V conduction time are neither antagonistic, synergistic, nor additive.

Effects upon intraventricular conduction time. Hyperkalemia alone produces definite impairment of intraventricular conduction, but doubling of the normal QRS time of approximately 0.04 second was not observed in these experiments until the level of plasma potassium exceeded 6.5 mEq. per liter. With a higher concentration of plasma potassium the QRS time may exceed 0.16 second. All of these data are presented in Fig. 4. When quinidine alone was infused, prolongation of the QRS time was also produced but not to the same degree seen with hyperkalemia. The highest levels of quinidine achieved did not produce a QRS duration greater than 0.10 second. The complete data on quinidine are presented in Fig. 5. The data from the experiments in which both potassium and quinidine were infused are also presented in Fig. 5.

The intraventricular conduction times of those dogs in which the plasma potassium exceeded 6.5 mEq. per liter are shown by open circles. Reference to Fig. 4 will show that the intraventricular conduction times of these dogs (i.e., those receiving quinidine and having levels of potassium above 6.5 mEq. per liter) do not differ essentially from the intraventricular conduction times of dogs in which hyperkalemia of comparable degree was produced without simultaneous infusion of quinidine. Thus, quinidine does not alter potassium-induced prolongation of intraventricular

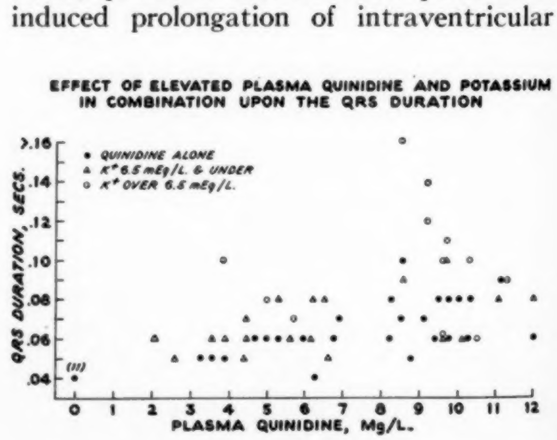

Fig. *5*. The QRS duration of those animals with potassium over 6.5 mEq. per liter should be compared with the QRS duration of animals infused with potassium only, as shown in Fig. 4.

conduction time. The intraventricular conduction times of those dogs in which the plasma potassium was 6.5 mEq. per liter or below are shown by open triangles. It is apparent from the data in the graph that the intraventricular conduction time in these animals is little, if any, more prolonged than that in those to which quinidine alone was given. Thus, when the lower degrees of hyperkalemia are considered, potassium and quinidine are neither antagonistic, synergistic, nor additive in their ability to produce impairment of intraventricular conduction.

Discussion

The initial question can now be answered. The effects of hyperkalemia and of high levels of quinidine upon intra-atrial, atrioventricular, and intraventricular conduction are neither additive nor synergistic. Thus, in patients with hyperkalemia, one would not expect exaggeration of the toxic effects of quinidine as manifested by cardiac conduction defects. On the basis of these studies, hyperkalemia per se is no contraindication to quinidine therapy.

These experiments do not throw any light upon the basic mechanism whereby either potassium or quinidine affect transmission of the excitatory process within the heart. Neither can one make a reasonable inference concerning whether one or more than one mechanism is involved. This follows from the fact that regardless of whether they affected the same or different mechanisms, one would hypothecate that their effects would at least be additive.

Summary

Normal dogs were infused with potassium chloride solution and with quinidine sulfate solution separately and in combination. Concentrations of serum potassium and of plasma quinidine were determined. Effects upon P waves, together with intra-atrial, atrioventricular, and intraventricular conduction times, were determined. Both quinidine and hyperkalemia produce prolongation of all three parameters of conduction velocity within the heart. These effects are neither additive nor synergistic.

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The effect of intracavitary carbon dioxide on surface potentials in the intact canine chest

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It has been suggested that the mass of blood in the cavities of the heart distorts the electrical field in the chest and introduces error into the voltages recorded in electrocardiographic leads.[1-3] Theoretically, a nearby dipole with its axis directed radially from the blood-filled cardiac cavity will produce a greater voltage in surface leads than if the mass of blood were replaced by a medium of lesser electrical conductivity. This prediction may be extended to waves of activation moving away from the cavities: the presence of the blood is expected to enhance the peripheral effect, thus amplifying the resultant deflections in appropriate electrocardiographic leads.

In contrast to the heightened voltage from a *radial* dipole near a region of greater conductivity, the peripherally detected difference in potential from a dipole with its axis *tangential* to the boundary of the better conducting region should be reduced. Such theoretical expectations have been demonstrated easily in two dimensions with conducting paper, as noted in the Appendix of this report. With such two-dimensional models, the effect of a region of increased conductivity on a nearby dipole was compared with the distribution of potential in a homogeneous medium, and—when a hole was cut in the conducting paper—the theoretical prediction for completely removing the region of greater conductivity was seen. The effect on nearby dipoles under such circumstances was now reversed: the peripheral voltage from the radial dipole was diminished, and from the tangential dipole magnified.

The present study concerns the extension of these predictions to three dimensions and the living animal by replacing the good conductor (blood) in the ventricular cavities by a poor conductor (carbon-dioxide gas). Separation between the contributions of radially directed excitation in the muscle surrounding each ventricular cavity was in this manner sought and in large part found. The removal of the shunting effect

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of blood made possible the additional distinction between probable radial spread of excitation during normal depolarization and probable tangential spread of excitation during right bundle branch block.

Methods and materials

Fifteen mongrel dogs which weighed between 9.0 and 19.5 kilograms were anesthetized with intravenous sodium pentobarbital (30 mg. per kilogram of body weight) and placed supine on the fluoroscopy table. Electrocardiograms were recorded with standard and augmented unipolar limb leads and unipolar chest leads; spatial vectorcardiograms were recorded by both the equilateral tetrahedral reference system (Wilson-Burch[4]) and the lead-field system (McFee-Johnston[5]). Recordings were made with a DuMont 321-A oscilloscopic camera mounted on a dual-beam slave oscilloscope driven from two Hewlett-Packard 130B oscilloscopes; signals from surface electrodes were amplified by Tektronix 122 preamplifiers. The front and back electrode grids for the McFee-Johnston system were each made of five 1-cm. brass discs mounted to form a 2-inch square (between the centers of the four outer discs) on polyethylene sheeting and connected by 20,000-ohm resistances.* The lateral lead pairs were composed of foreleg and axillary electrodes joined by 8,000-ohm resistances; head and foot electrodes were without added resistances, and the Wilson central terminal electrodes were connected by 12,000-ohm resistances.

Cardiac catheters were introduced by jugular or femoral vein and carotid or femoral artery into the right and left ventricles, respectively. Before each insufflation the animal was placed in the 45-degree Trendelenburg position. A quantity of 30 to 50 c.c. of gaseous carbon dioxide, as required to fill each ventricle by fluoroscopic estimate, was introduced first into the right ventricle, then into the left ventricle, and then into both ventricles simultaneously. Selected electrocardiographic and vectorcardiographic tracings (usually including the horizontal plane projection or its components as the most sensitive parameter of change in distribution of thoracic potential) were recorded serially or continuously. In order to consider an experiment satisfactory, we required a return of the depolarization complex to the previous normal pattern before bilateral insufflation of carbon dioxide was attempted.

In 5 dogs, right bundle branch block was induced by the injection of formaldehyde by percutaneous needle into the right septal myocardium under fluoroscopic and electrocardiographic guidance. When the tip of the needle (introduced through the second left intercostal space parasternally) was demonstrated to touch the catheter, the right septal wall was pricked or scratched until a right bundle branch block appeared on the monitoring oscilloscope; then 0.5 to 1 c.c. of 40 per cent formaldehyde was injected at the site. The lesion was verified at autopsy by iodine-staining of the bundle.[7] The observations with infusion of carbon dioxide were then repeated in the presence of the right bundle branch block. Left-sided or bilateral instillations of gas were omitted on two occasions prior to the induction of the right bundle branch block, so as to minimize the hazards to which the animal was subjected.

Results

The "normal" ventricular depolarization potentials during right ventricular filling with carbon dioxide. The effect on surface potentials of filling the right ventricular cavity with carbon dioxide, as visualized by electrocardiogram and spatial vectorcardiogram, may be seen in Figs. 1 and 2, which are representative of the findings in this study. The transformation in the depolarization complex can be followed most clearly in the horizontal plane projection of the spatial vectorcardiogram but can be seen readily in the sagittal lead of the other graphic form. The peak of the ventricular filling, as seen through the fluoroscope, coincided with the maximum degree of shrinkage of the R wave of the QRS complex. In the spatial vector loop the very earliest and the very latest portions of depolarization were unchanged, and the maximum apparent change occurred between early and middle and between mid-

*Since the masses of the dogs were expected to be roughly one eighth of those of adult men, the linear dimensions of the grids were constructed $3\sqrt{1/8}$ or 1/2 of those recommended for men.[6]

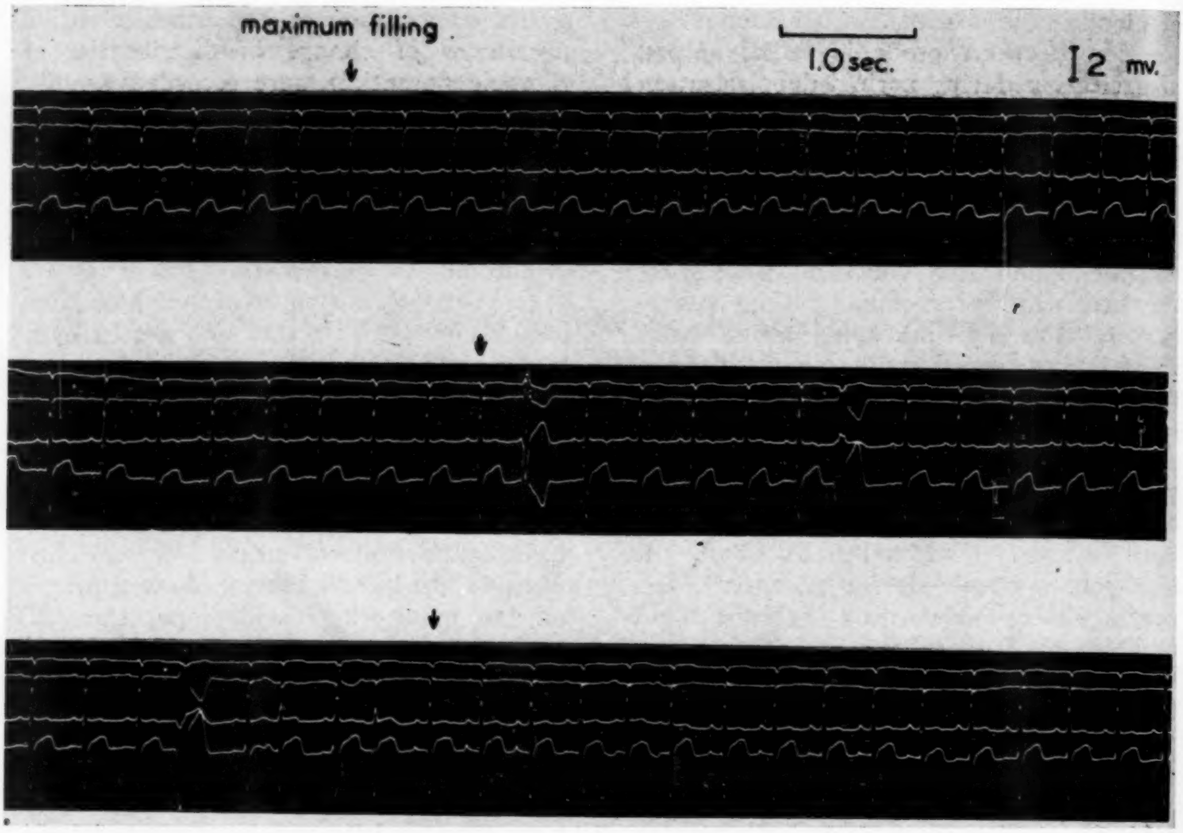

Fig. *1*. Simultaneous electrocardiograms of Dog No. 15 made during right ventricular (*top*), left ventricular (*middle*), and biventricular (*bottom*) insufflation with CO_2. The leads from above downward in each group are unipolar back inverted, bipolar left-right, bipolar foot-head, and bipolar front-back. (For convenience the sign is arranged so that the leads may be read as analogous to clinical Leads V_8 inverted, V_F, I, and V_1.) Note that the anterior precordial R diminished with either right or left ventricular insufflation of CO_2 and disappeared completely when both ventricles were filled with gas.

dle and late depolarization. However, specific loss of forward components actually characterized the whole intermediate period, as determined by superimposing electrocardiograms and vectorcardiograms.

The shrinkage of peripherally recorded voltages began to subside almost immediately, and the previous normal patterns routinely reappeared within 5 to 10 seconds as the carbon dioxide was expelled into the pulmonary artery. Frequently, one or more premature ventricular systoles occurred just after maximum filling.

The "normal" ventricular depolarization potentials during left ventricular filling with carbon dioxide. The immediate peak electrocardiographic effects were more transient with injection of carbon dioxide into the left ventricular cavity, and a greater amount of carbon dioxide was required to maintain even a transient radiolucency of the entire ventricular cavity than on the right (usually 50 c.c. as compared with 30 c.c.). Since the cavities approximated each other in volume when cast postmortem, this discrepancy was attributed to relatively more powerful and efficient emptying by the left ventricle. An altered configuration of the spatial vector loop consistently different from that of right-sided insufflation was observed at the height of left ventricular filling with carbon dioxide: voltages during middle depolarization were drastically curtailed, and a distinctive gouge indented the horizontal plane projection of the QRS spatial vector loop more from the left than from the front (Fig. 2).

Emptying of carbon dioxide from the left ventricular cavity was frequently followed within 15 to 30 seconds by the development of "ischemic" T waves and spatial vector loops, S-T shifts, and then

QRS alterations usually characterized by removal of posteriorly directed contributions during the later one half of depolarization (Fig. 3). If the animal had been quickly brought out of the Trendelenburg position after peak filling with carbon dioxide, these changes faded over a period of 10 to 15 minutes, without residual. However, repeated infusion of the left side was usually poorly tolerated and resulted in either ventricular fibrillation or longer lasting deformities of the QRS and elevations of the S-T segment which required several hours to fade. After a series of left ventricular insufflations, one animal died during the night.

The normal ventricular depolarization potentials during combined left and right ventricular filling with carbon dioxide. Because of the unfavorable sequelae frequently experienced after insufflation of the left ventricle alone, only on 5 occasions were successful simultaneously bilateral injections of carbon dioxide accomplished. In Fig. 2, two series of horizontal plane projections of the spatial vectorcardiogram are seen, illustrating the respective reductions in the QRS spatial loop with first right, then left, then bilateral ventricular filling with carbon dioxide. It should be noted that neither right nor left insufflation appeared to alter greatly the very early frontward component of depolarization, but insufflation of both chambers removed most of it. Although the QRS complexes and loops were reduced markedly, as though in an additive manner, they did not disappear entirely.

Bilateral infusion was usually followed by the more or less transient "ischemia"

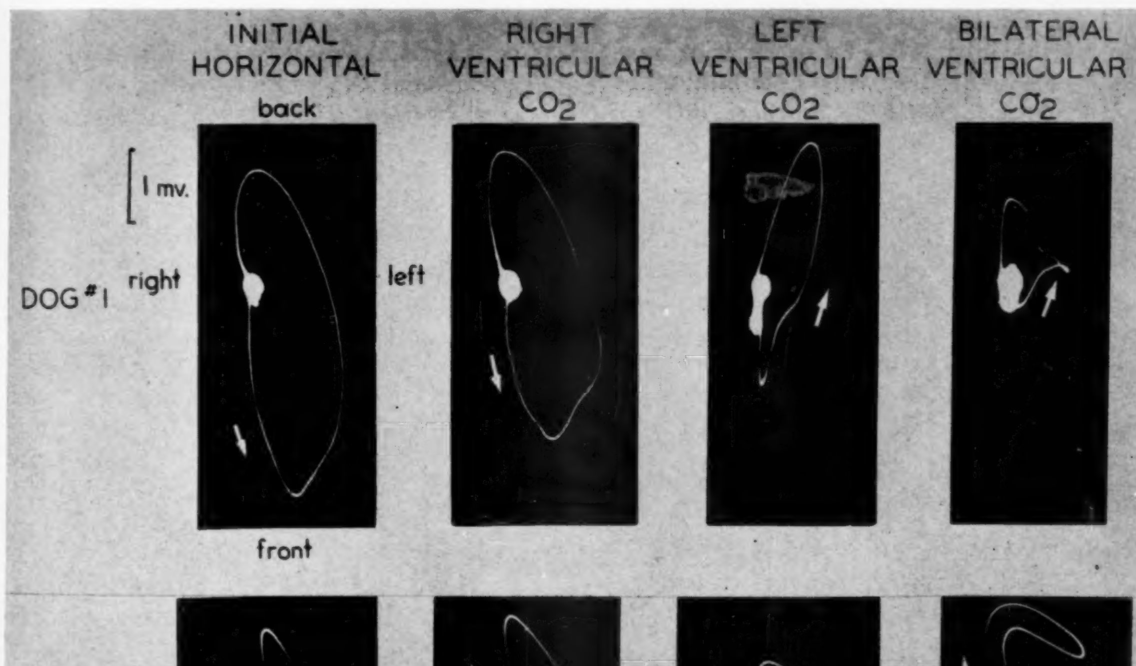

Fig. 2. Serial projections of the horizontal plane of the vectorcardiogram (lead-field system) during successive insufflation with right ventricular, left ventricular, and biventricular CO_2 in Dogs No. 1 and 3. Note the removal of early frontward portions of the depolarization complex during each instance of right ventricular insufflation, and backward displacement of the late QRS spatial vector loop. With left ventricular insufflation of CO_2, more of middle depolarization is removed (especially laterally), and with combined insufflation the losses appear to be additive. The trace has been made lighter in portions of the first three prints (Dog. No. 1) to facilitate photographic reproduction.

and "injury" effects previously noted for the left ventricular infusion.

The effect of intracavitary carbon dioxide upon the potentials found with right bundle branch block. Two significant differences were observed during insufflation of carbon dioxide after the induction of right bundle branch block. The first difference was that the late potentials of depolarization expanded rather than shrank in recorded voltage when the *right* ventricle was filled with gas (Fig. 4). This was most manifest in the increased amplitude of the right precordial R′ on the electrocardiogram or forward enlargement of the whole circular "block" portion of the QRS spatial vector loop in 4 of the 5 instances. In the fifth dog with right bundle branch block, expansion occurred along the left-right axis rather than along the front-back axis (Fig. 5). The second finding was a marked shrinking away of the earliest frontward voltages (i.e., of the initial R of the anterior precordial electrocardiogram) upon filling of the *left* ventricle with carbon dioxide (Figs. 4 and 5).

Discussion

Reduction in the right ventricular epicardial R wave during insufflation of the right ventricular cavity by dielectrics, such as gas or mineral oil, had been observed by Oppenheimer and associates.[8] They attributed this loss to an insulating effect of the dielectric, which shielded the electrode from the *left* ventricle. Comparable conclusions were drawn for the effects on other leads and were tied to the "zone of interference" theory of electrocardiographic genesis of Nahum and Hoff.[9,10] The zonal theory apparently arose from equating epicardial breakthrough at any ventricular topographic locus with the process of activation of the entire wall at that site. As a result, major electrical contributions at a given instant in the depolarization cycle were attributed to regions of myocardium from which the last vestige of electrical activity was just disappearing. The work of Scher[11] and Durrer[12] leaves little doubt now about the existence of large wave fronts moving generally from endocardium to epicardium during ventricular depolarization. Thus, the explanation of changes in peripheral voltage during such further alteration of the already inhomogeneous thoracic volume conductor as provided by insufflation of carbon dioxide must be found by relating the physical distribution of potential in the conductor to the instant-to-instant configuration of the wave fronts of depolarization.

The finding of reduction by right ventricular intracavitary gas in the recorded voltage during normal depolarization, and amplification during bundle branch block, confirmed the theoretical predictions of Brody[1,2] and Nelson[3] on the effect of intracavitary blood. As noted in the Appendix, the presence of a nearby mass of decreased resistivity (blood) may be expected to amplify the peripheral effect of radially directed dipoles, but to reduce that of tangentially directed dipoles or waves of activation. By contrast, the presence of a nearby mass of increased resistivity (gas) may be expected to reduce the peripheral effect of radial dipoles, but exaggerate that of tangential dipoles or of the tangential spread of excitation.

The introduction of carbon dioxide selectively into the ventricular cavities provided a means of dissecting right from left ventricular contributions to the total record of depolarization. Thus, as seen in Fig. 2, in the presence of normal conduction, the placing of gas in the right ventricle reduced anteriorly directed contributions from early in depolarization to moderately late (note the backward displacement of the later portion of the spatial vector loop); careful comparison between initial and altered precordial leads and loops showed that this loss was continuous from early to late depolarization and not an intermittent loss. Left ventricular filling with gas produced a more drastic loss in middle depolarization; the fact that the loss was not greater from "removal" of the greater ventricle may be related to a rapid attenuation of the dielectric effect with increasing distance from the cavity. Thus, doublets or waves of activation in the outer shell of the relatively thick-walled left ventricle may have been relatively unaffected by the presence of gas. Although neither right nor left ventricular insufflation was sufficient, the combination of right and left ventricular insufflation of carbon dioxide almost completely removed all anteriorly

directed activity during depolarization. Similarly, when normal early right ventricular depolarization was removed by bundle branch block, left ventricular insufflation sufficed (Fig. 6) to remove the remaining early frontward components—graphically demonstrating the fusion of left septal and right ventricular activation to form the normal right precordial R wave. The ability to remove from consideration right ventricular contributions to the QRS complex should greatly facilitate the more exact assay of the effect of experimental left ventricular myocardial lesions, such as those produced by fixation with the injection of formaldehyde.[13]

The fact that the expansion of the voltages of late depolarization in the right bundle branch blocks occurred along the front-back axis of the chest rather than along the left-right axis in all except one animal was somewhat unexpected. Abnormal depolarization of the right ventricular myocardium which resulted from right bundle branch block might have been predicted to be directed largely from left to right if tangential to the right ventricular cavity. However, since the right ven-

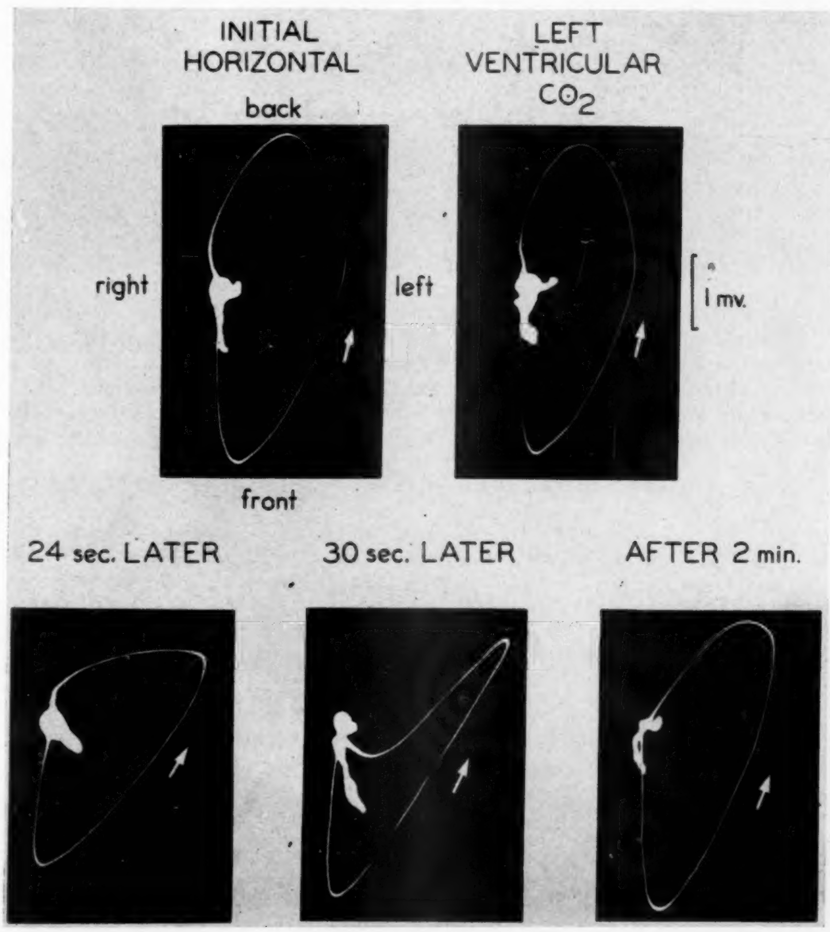

Fig. *3*. Serial projections of the horizontal plane vectorcardiogram (lead-field system) during insufflation of CO_2 into the left ventricle and subsequently in Dog No. 8. The second record was made just after the peak of lucency and is less drastically reduced than the immediately preceding beat not shown. Note the enlargement of the T loop and the S-T-segment shift which developed well after the gas had been expelled from the right ventricle. The QRS loss at the height of "ischemia" was of posteriorly directed components in the later one third of depolarization, in contrast with the immediate lateral loss in middle depolarization when gas was still in the left ventricular chamber. The trace has been made lighter in portions of the prints in this figure to facilitate photographic reproduction.

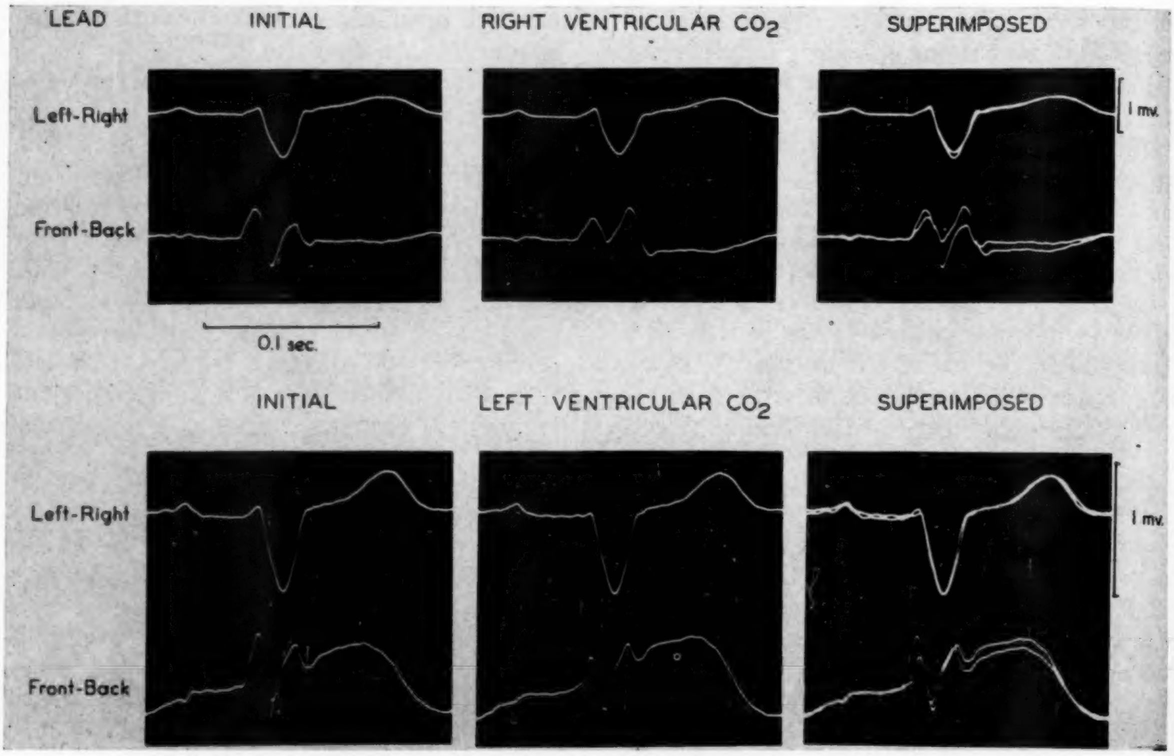

Fig. *4*. A comparison of right and left ventricular insufflation of CO_2 in the presence of experimental right bundle branch block, in Dog No. 7. In each pair of simultaneous tracings the upper lead is Lead I, and the lower lead is the unipolar anterior chest lead presenting the conventional RSR′ pattern of RBBB. The top row of prints shows successively the control tracing, the tracing at maximum right ventricular lucency, and the two tracings superimposed. The bottom row shows the control, the maximum left ventricular CO_2- effect, and the two superimposed. Note that gas in the right ventricle resulted in an expanded R′, but gas in the left ventricle greatly reduced the initial R.

tricular surface of the canine heart frequently faces slightly to the left as well as ventrally, tangential spread through the right ventricular free wall would thus frequently move toward the front of the chest as well as to the right.

Alternative explanations for the changes in the pattern of depolarization complexes when intracavitary gas was present were considered. An alteration of the membrane potentials which results from change in degree of stretch on the myocardial fibers when contracting against gas rather than blood is a theoretically possible mechanism for deforming the QRS complex acutely. However, alteration of the initial mechanical tension on rat atrium has been reported to produce no detectable changes in the membrane potentials.[14] Anatomic rotation of the heart as a result of either a dilating effect or a shifting of the center of gravity of the heart could account for some of the differences, but no great positional change was actually seen fluoroscopically. A stretching of the right bundle to interfere with conduction might have been considered had the gas been injected under sufficient pressure to produce right ventricular dilatation; however, this possibility was precluded by the observations in which complete right bundle branch block had already been produced. A biochemical alteration from the reaction of carbon dioxide with surface membranes is a possible immediate cause for the change in electrical pattern, but no lag was noted: the maximum electrical effect occurred with maximum fluoroscopic lucency and disappeared when the gross gas disappeared from the ventricle each time.

However, with the left ventricular insufflation another real cause for the development of drastic alterations in the QRS complex and spatial loop became apparent from 15 to 30 seconds *after* the maximum fluoroscopic left ventricular lucency; QRS

deformation occurred accompanied by shifts of the S-T segment and ischemic T-wave changes. Quick removal of the animal from the Trendelenburg position seemed to reduce the subsequent duration of these effects. These sequels, perhaps attributable to the coronary embolization of gas, presented little problem in differentiation from the instantaneous change in peripheral voltages accompanying the peak of left ventricular filling with the gas. Both the times of occurrence and the patterns were characteristically different (Fig. 3). Oppenheimer and associates[15] instilled gaseous carbon dioxide by fine catheter into a coronary artery, without occlusion and without ill effect. As contrasted with such benign nonocclusive coronary instillations, transient but complete coronary artery occlusions with bubbles of gas (which may by exchange include oxygen and nitrogen in addition to carbon dioxide) seemed the likely cause for the ischemic sequels observed by us.

Summary

A reversal of the manifest electrocardiographic effects of the intracavitary blood mass was produced by selectively instilling carbon dioxide into the right ventricle, the left ventricle, and then both chambers in mongrel dogs. In 5 dogs the experiment was

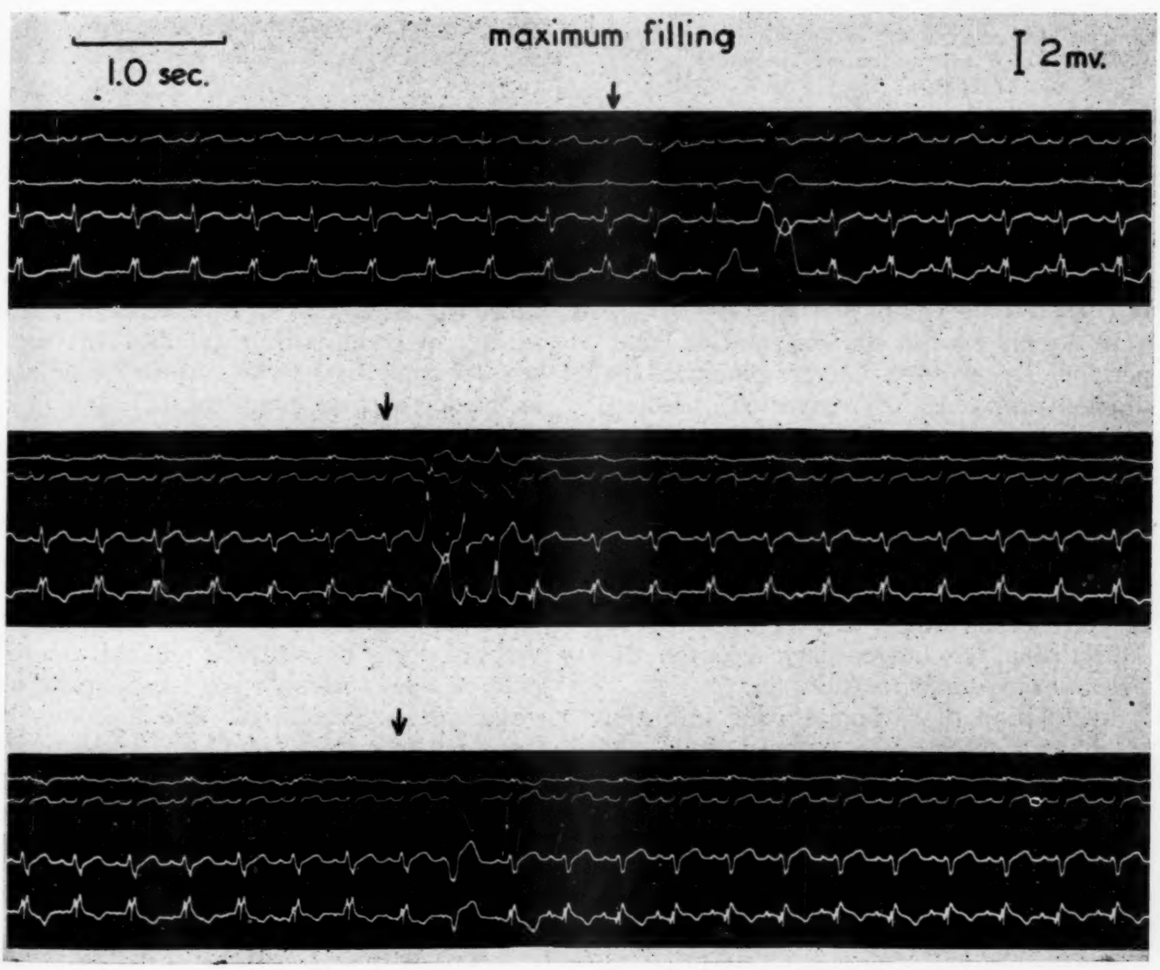

Fig. 5. Simultaneous electrocardiograms of Dog. No. 15 made during right ventricular (*top*), left ventricular (*middle*), and biventricular (*bottom*) insufflation with CO_2—all after the induction of RBBB. The leads from above downward in the second and third groups are unipolar back inverted, bipolar left-right, bipolar foot-head, and bipolar front-back. In the first group the bipolar left-right appears above the inverted unipolar back lead (see Fig. 1). Note that left and bilateral ventricular CO_2 greatly reduced the initial R in the front-back lead, but, in contrast to Fig. 4, right ventricular CO_2 did not expand the R′—although it did expand the S in the left-right lead. The bilateral fillings were not completely simultaneous front-back, as can be seen by the fact that the left-right S expansion followed the initial R loss.

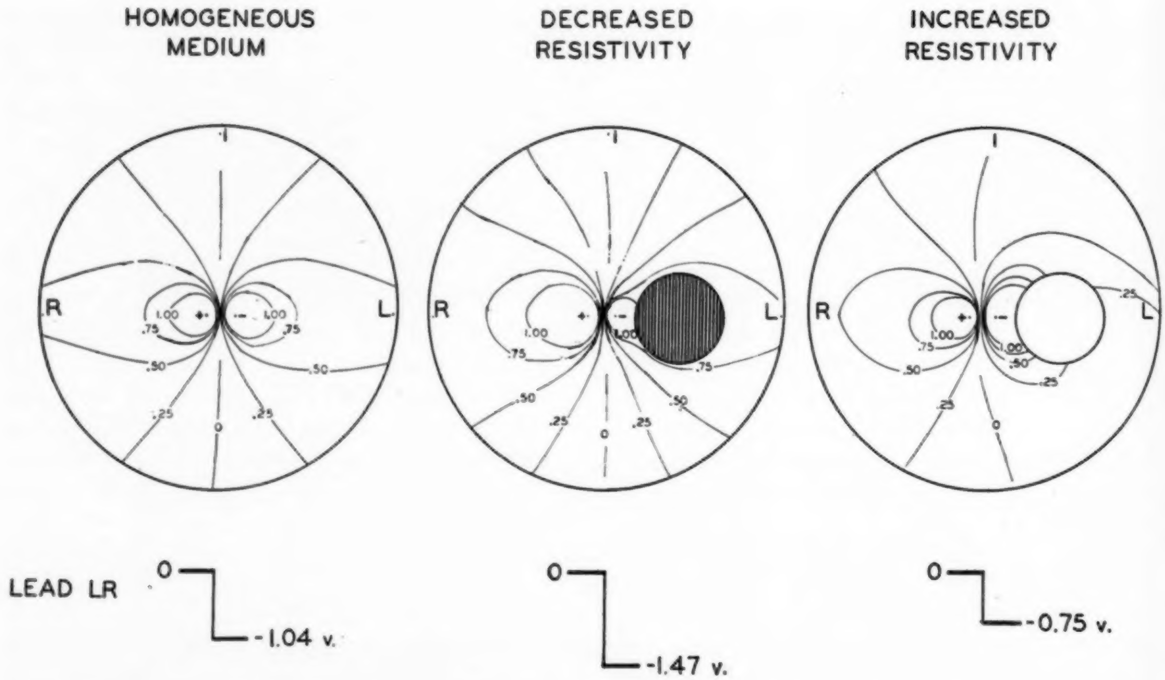

Fig. 6. The effect on distribution of potential in a two-dimensional plot of altering "cavity" resistivity with the axis of the dipole directed radially from the cavity. See Appendix for details.

repeated after the percutaneous induction of right bundle branch block.

In keeping with the expectation that peripherally recorded voltages generated by dipoles or waves of activation directed radially from the gas-filled cavity would be diminished, curtailment of the QRS complex and spatial vector loop was found during normal depolarization. But in the presence of right bundle branch block the "block" portions of the tracings increased in peripheral voltage, in keeping with the expectation for tangentially oriented dipoles or waves of activation.

Insufflation of carbon dioxide into the right ventricular cavity reduced anteriorly directed components in the recordings of surface potentials from moderately early to moderately late in depolarization; insufflation of carbon dioxide into the left ventricular cavity reduced laterally directed components, especially in middle depolarization. Further reduction was noted with bilateral insufflation, with especially prominent loss of almost all initial anteriorly directed components. Similar loss of both septal and right free wall components of the anterior precordial R occurred during right bundle branch block with left ventricular insufflation.

Selective ventricular insufflation with carbon dioxide provides a means of separating, in great part, right and left ventricular contributions to surface recordings in the dog with an intact chest.

Appendix

Fig. 6 shows the results of three experiments of mapping isopotential lines and measuring lead voltage in an idealized two-dimensional system with conducting paper. In each instance a potential drop of 12 volts of direct current was applied to a dipole of 2 pins which were 1 cm. apart, as designated in the discs. The first disc is homogeneous; the second has a small circular area of decreased resistivity produced by painting in the area of the circle with conducting silver ink; and in the third disc in the same site the circle has been cut out, leaving an empty hole or "cavity" of extreme resistivity.

Mapping was made with the exploring pin connected to one post of a direct-current voltmeter and the reference pin at point (i) connected to the other post. The direction of flow of current between elements of the dipole may be considered to be perpendicular to the isopotential lines. The voltage registered in a bipolar surface

lead LR, made by connecting the opposing pins to the voltmeter, has been represented diagrammatically below the discs, as though it were impressed on an electrocardiographic record.

Note that the good conductor extended the region of high potential a greater distance along the axis of the radial dipole, and that, thus, with the silvered circle the peripheral registration of voltage was enhanced. However, when the circle was cut out, leaving the region highly resistive, transfer of high potential along the axis of the radial dipole was impaired by the new boundary, and the peripheral registration of voltage was diminished. By analogy, we may expect intracavitary blood to enhance the surface effect of radial electrical activity,[1-3] and intracavitary carbon dioxide to reduce it.

Comparison of Fig. 7 and Fig. 6 illustrates the reversal of such effects merely by having the dipole oriented in a direction tangential to the boundary of the cavity rather than radial to it. Note that now the good conductor reduced the registration of peripheral voltage, and the poor conductor increased it.

The possibility that the dipole moment itself may be altered by nearby changes in the conducting medium was considered. Such an alteration in dipole moment could thus be responsible for the peripheral changes noted. To examine this possibility the experiments were carefully repeated with measurement of the interpolar resistance at each step. The peripheral results with silvering or cutting out the inner circle were just as before, but the change in the interpolar resistance never exceeded 1.1 per cent.

We are grateful to Dr. Leon Churney for his review of this manuscript as well as his encouragement and suggestions.

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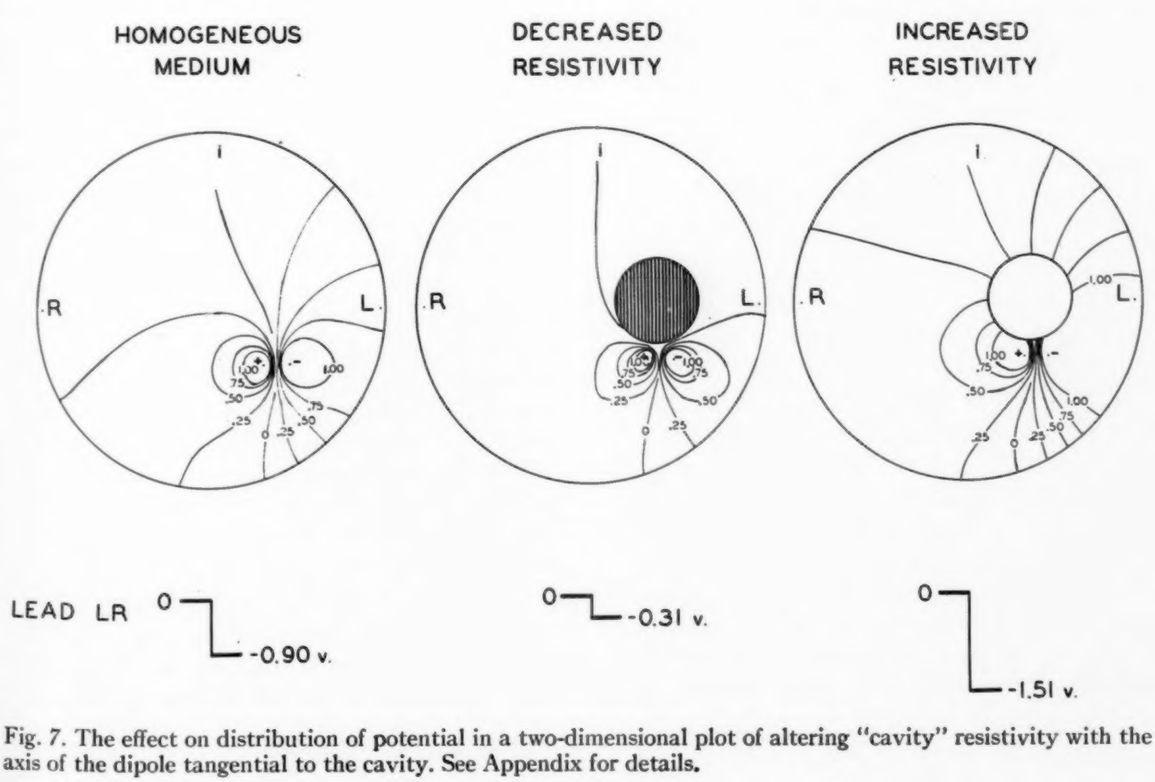

Fig. 7. The effect on distribution of potential in a two-dimensional plot of altering "cavity" resistivity with the axis of the dipole tangential to the cavity. See Appendix for details.

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Vascular lesions in experimental pulmonary embolism

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The experimental production of pulmonary vascular lesions has received growing attention since 1948, when Harrison[1] published his results on heterologous clot embolism in rabbits. Numerous reports have since appeared, based on experiments with different species of animals and a great variety of methods.[2] The lesions described differ in detail according to the species and the techniques used, but, disregarding those differences, most published results can be summarized as shown in Table I. It can be seen from this table that, although all lesions can appear as the effect of pulmonary hypertension, some of them may also result from different mechanisms, such as multiple pulmonary embolism or hypersensitivity.

The application of these observations to human subjects with pulmonary vascular lesions raises the question of separating the effects of pulmonary hypertension from those of other injurious agents, and especially from those of multiple embolism. Thus, one can find in the literature cases of pulmonary arteritis attributed to pulmonary hypertension, to multiple embolism, to hypersensitivity, to rheumatic fever, or to a combination of these factors.[3] Many of the papers on multiple embolism produced by blood clots contain no information on pulmonary arterial pressure. On the other hand, Thomas and O'Neal[4] produced chronic blockage of the pulmonary circulation by means of multiple emboli of plastic beads that resulted in dilatation and hypertrophy of the right ventricle (used by these authors as proof of pulmonary hypertension), without vascular lesions in the lungs.

Table I. *Pathogenesis of experimental pulmonary vascular lesions**

Lesion	*Pathogenesis*
Intimal thickening	Multiple thrombi embolism Pulmonary hypertension
Medial hypertrophy	Pulmonary hypertension
Muscularization of the arteriolar media	Pulmonary hypertension
"Plexiform" or "angiomatoid" lesions	Multiple thrombi embolism (?) Pulmonary hypertension (?)
Arteritis or arteriolitis with or without necrosis	Multiple thrombi embolism Cotton embolism Hypersensitivity Pulmonary hypertension

*For bibliography, see Reference 2.

On the basis of the data previously mentioned, an experimental situation was planned in which the anatomic effects of pulmonary hypertension could be clearly separated from the effects of multiple

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Table II. *Distribution of animals*

Group	*Number of animals*	*Emboli*	*Site of injection*	*Schedule of injection*	*Sacrifice time*	*Purpose*
A	6	Fibrin clots	Left pulmonary artery	5 injections at 2-week intervals	15 days after the last injection	Fibrin effect on the vascular wall, eliminating the possible effect of pulmonary hypertension
B	6	Fibrin clots	Peripheral vein	5 injections at 2-week intervals	15 days after the last injection	
C	6	Plastic beads	Left pulmonary artery	5 injections at 2-week intervals	15 days after the last injection	Effect of the possible pulmonary hypertension without fibrin or blood
D	6	Plastic beads	Peripheral vein	5 injections at 2-week intervals	15 days after the last injection	
E	6	Whole blood clots	Left pulmonary artery	Weekly injections for 5 weeks	7 days after the last injection	Effect of whole blood on the vascular wall separating the possible effect of pulmonary hypertension
F	7	Whole blood clots	Left pulmonary artery	Injection	2, 4, 20, 36, 48, and 72 hours after the injection	Early stages in the evolution of the embolic pulmonary vascular lesions

emboli. The aim of this paper is to report the results obtained in a series of experiments in which multiple unilateral pulmonary embolism was produced in dogs with autologous whole blood clots, autologous fibrin, and inert plastic beads. The dog was chosen for these experiments because it has been shown that in this animal pure sustained pulmonary hypertension can produce vascular lesions, and because cardiac catheterization can be easily performed.

Material and methods

1. Animals. Thirty-seven young mongrel dogs of both sexes were used. Their average weight was 40 pounds. They were kept in separate cages throughout the experiments and were fed a standard diet. The 37 dogs were divided into 6 groups, each receiving a different treatment, according to Table II.

2. Preparation of emboli. Three types of emboli were utilized: fibrin clots, whole blood clots, and plastic beads.

FIBRIN CLOTS. The technique used for the preparation of fibrin clots was essentially that of Barnard.[5]

BLOOD CLOTS. Twenty milliliters of whole blood was allowed to clot in a test tube. The clot was finely cut until the fragments passed easily through a No. 18 gauge needle, suspended in saline, and injected through the catheter.

PLASTIC BEADS. Lucite plastic beads,* 50 to 150μ in diameter, were injected according to the technique used by Thomas and O'Neal.[4] The amount of plastic beads injected was equivalent in volume to two thirds of the clots, which was thought to result in approximately the same degree of obstruction to the pulmonary circulation as that produced by either whole blood or fibrin clots.

3. Catheterization technique. In Groups A, C, E, and F, unilateral pulmonary embolism was carried out by means of cardiac catheterization. The animals were anesthetized with intravenous pentobarbital (35 mg./Kg. of weight). Each of the branches, as well as the main trunk, of the external jugular vein on each side was used for one catheterization, allowing therefore

*Obtained through the courtesy of Dupont de Nemours, Wilmington, Del.

Fig. *1.* Organized thrombus in the lumen of a large pulmonary artery. The intima is thickened probably as the result of previous embolization. Aldehyde-fuchsin and Van Gieson, ×200.

six possibilities for catheterization of each dog. When thrombosis or cicatrization did not allow completion of five catheterizations at the level of the neck, the axillary vein was used. Under fluoroscopic guidance a No. 8 Cournand catheter was introduced into the left branch of the pulmonary artery. Blood clots or plastic beads were then slowly injected, followed by 10 ml. of saline solution to wash the catheter. Animals of all groups, except those of Group F, were injected during the following three days with 150,000 units of procaine penicillin every 12 hours.

4. Handling of the lungs. Animals were sacrificed by rapid intravenous injection of 500 mg. of Kemithal. Complete autopsies were performed. The heart and lungs were separated together from the thoracic cavity and fixed by intratracheal injection of 10 per cent formalin; they were kept in containers with the same fixative.

Representative (2 to 8) sections were taken from each lobe of the left lung and from the right lower lobe. They were embedded in paraffin, sectioned, and stained with hematoxylin-eosin, Gömöri's fuchsin-paraldehyde for elastic fibers, and Foot's stain for reticulum and collagen.

Results

Autopsies of the sacrificed animals did not reveal macroscopic alterations either in the lungs or in the heart. The right ventricular and auricular walls of the heart were carefully examined and measured, and no differences were found from hearts of normal animals. However, a definite decision in this respect is not easy since there were wide variations in breed and weight. The histologic changes are discussed first, and their distribution in the different groups of animals is then presented.

Microscopic changes. The microscopic lesions found were: (1) blood clots at various stages of organization in the lumen of the arteries, (2) vacuolation of the endothelial cells that were in direct contact with the clots, and (3) arteriolitis. In the following paragraphs each one of these lesions is described and their distribution

Fig. *2.* Polypoid formation in a medium-sized artery. Aldehyde-fuchsin and Van Gieson, ×180.

Fig. *3*. Focal fibrous intimal thickening of a large pulmonary artery. Verhoeff-Van Gieson, ×230.

in the different groups of animals is examined.

BLOOD CLOTS. Blood clot emboli were found especially in vessels that were over 100μ in diameter, always with a well-individualized external elastic membrane, and in the vicinity of bronchi or bronchioles. Most thrombi were in an advanced stage of organization, with deposits of connective tissue and vascular neoformation (Figs. 1 and 2). Other than the endothelial vacuolation, which is discussed below, only occasional lesions were found in the wall of the vessels; in two of them, coinciding with the site of implantation of the thrombus, there was destruction of the elastic membrane and substitution of the media by connective tissue, which continued the connective tissue of the organized clot (Fig. 3). Focal fibrotic thickening of the intima was rarely found, and probably corresponded to well-organized and endothelial-covered clots (Fig. 4).

ENDOTHELIAL VACUOLATION. This was a constant finding, although of variable intensity. The endothelial cells in intimate contact with the clot had a swollen aspect, the cytoplasm being occupied by a large vacuole, unstained with the techniques used. The nuclei had a peripheral position, simulating "signet-ring" cells (Fig. 5). Elastic fiber stains showed clearly that the alteration was under the limiting internal membrane (Fig. 6). In most of the involved vessels the endothelium beyond the implantation site of thrombi had a normal aspect; in addition, most thrombi were of recent formation. As organization advanced, endothelial vacuolation became less apparent or was absent. Vessels of the same or larger diameter, without thrombi, showed a normal endothelium.

ARTERIOLITIS. The term arteriole is used throughout this paper in reference to vessels of small diameter, usually less than 50μ, situated away from bronchi or bronchioles, with only one internal elastic membrane and without muscular coat. Foci of inflammatory infiltration formed by polymorphonuclear leukocytes, lymphocytes, and macrophages, mixed with variable amounts of erythrocytes, were found

Fig. *4*. Embolus implanted in a medium-sized artery, with destruction of elastic and muscular fibers. Note absence of inflammation. Aldehyde-fuchsin and Van Gieson, ×180.

Fig. 5. Recent thrombus in a medium-sized artery. Endothelial cells in the top are swollen, vacuolated, and contain a slightly basophilic material. Hematoxylin-eosin, ×230.

only in the alveoli immediately surrounding the arterioles (Fig. 7). Transverse sections of arterioles showed that inflammatory cells surrounded the vessels in cuff-like fashion (Fig. 8). Within the groups of inflammatory cells, small clefts filled with red blood cells were seen, suggesting capillary proliferation; stains for reticulum fibers, however, showed that they had neither wall nor endothelial lining (Fig. 9). The arteriolar wall had a normal appearance; special stains revealed integrity of the elastic fibers (Fig. 10); rupture or alterations of the wall were not seen in any case. The observation of numerous sections revealed that there was a tendency for accumulation of inflammatory cells at the sites of arteriolar bifurcation (Fig. 11).

Distribution of microscopic changes in the different groups. In Group A, arteriolitis was found in all sections of the left lung, predominantly in the lower lobe. No alterations were seen in the right lung. In Group B, arteriolitis was found in both lungs in all animals, but the changes were few and small, and many sections had to be studied before the lesions were identified with certainty (Table III). Groups C and D, which received multiple plastic-bead emboli by way of the left pulmonary artery and by a systemic vein, respectively, showed no lesions of any kind. Finally, the results obtained in animals of Group E, to which autologous blood clots were given through the left pulmonary artery, are summarized in Table IV. It can be seen from this table that arteriolitis was predominant in the lower lobes, and that it was present despite the lack of organized thrombi in larger arteries. In Dog No. 4, vascular lesions in the right lung were interpreted as being caused by reflux of clots in one or more of the embolizations; the same alterations were found in the left lung. In the other animals belonging to this group no lesions were found in the right lung.

Animals of Group F received a single autologous thrombus embolization in the left lung and were sacrificed at intervals that varied between 0 and 72 hours after emboli-

Fig. 6. Partially organized thrombus in a large pulmonary artery, showing marked vacuolation of endothelial cells. Aldehyde-fuchsin and Van Gieson, ×250.

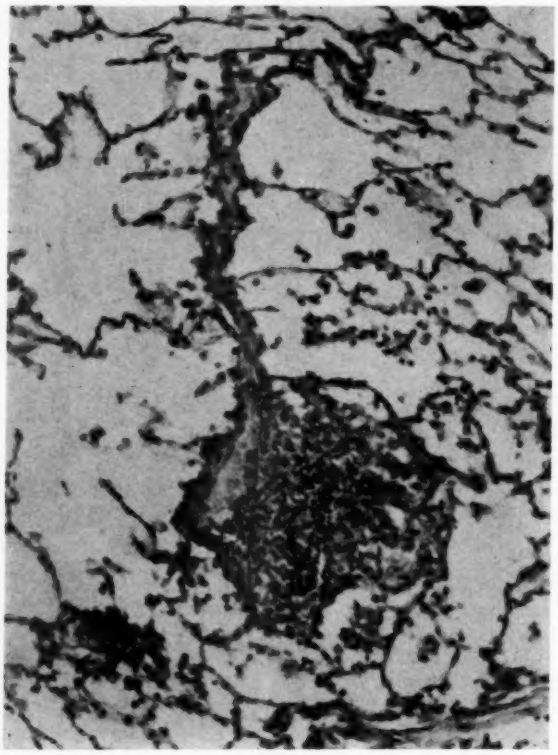

Fig. 7. Arteriolitis formed by lymphocytes, macrophages, and scarce polymorphonuclear leukocytes; there are few red blood cells between the inflammatory elements. The wall of the arteriole is normal. Hematoxylin-eosin, ×180.

zation. The microscopic findings are summarized in Table V. It can be seen that vacuolation of endothelial cells and arteriolitis appeared at 24 hours and persisted to the last observation, made 72 hours after embolization. A striking feature was that in the periarteriolar inflammatory nodules, more well-preserved erythrocytes were found among the cells than in similar lesions from animals of other groups.

Discussion

The results obtained in the present experiments indicate that repeated fibrin emboli or complete autologous blood emboli, when introduced into the peripheral veins or into the left pulmonary artery, produced several types of lesions in the pulmonary vessels in the dog. When the clots are made of whole blood, thrombi in different stages of organization are found in pulmonary vessels over 100μ in diameter. Focal fibrous thickening seen in some arteries of similar caliber may also be considered to be the result of organization and retraction of a clot that later on is covered by endothelium.[6,7] Only in two instances were lesions with destruction of the elastic fibers in the media of these vessels observed, and these were associated with organized thrombi. Lesions of the same type have been described in rabbits by Heard[8] and in rabbits and mice by Barnard.[5] Another type of lesion related to whole blood embolization is endothelial vacuolation, as first shown in the dog by Jacques and Hyman.[9] Undoubtedly, this type of endothelial alteration is related to the presence of clots, but its nature is

Table III. *Results in Groups A and B*

Animal number	*Group A*	*Group B*
1.	X	X
2.	X	X
3.	X	X
4.	+	X
5.	X	X
6.	+	X

+: Died during the experiment.
X: Arteriolitis.

Table IV. *Results in Group E*

Animal number	*Right lung*	*Left lung*		
		U.L.	*Lingula*	*L.L.*
1.	0	0	X	X
2.	0	+0	+X′	X′
3.	0	X	+X	+
4.	+X	X	X	+X
5.	–	–	–	–
6.	0	+	X	X

0: No lesions.
+: Organized thrombi in large vessels.
X: Arteritis in small arteries and arterioles.
X′: Extensive and intense arteritis.

Table V. *Results in Group F*

Sacrificed at	*Right lung*	*Left lung*
2 hr.	0	0
4 hr.	0	+
20 hr.	0	+
24 hr.	0	+X
36 hr.	0	+X
48 hr.	0	+X
72 hr.	0	+X

0: No lesions.
+: Recent thrombi in the lumen of large arteries.
X: Arteriolitis.

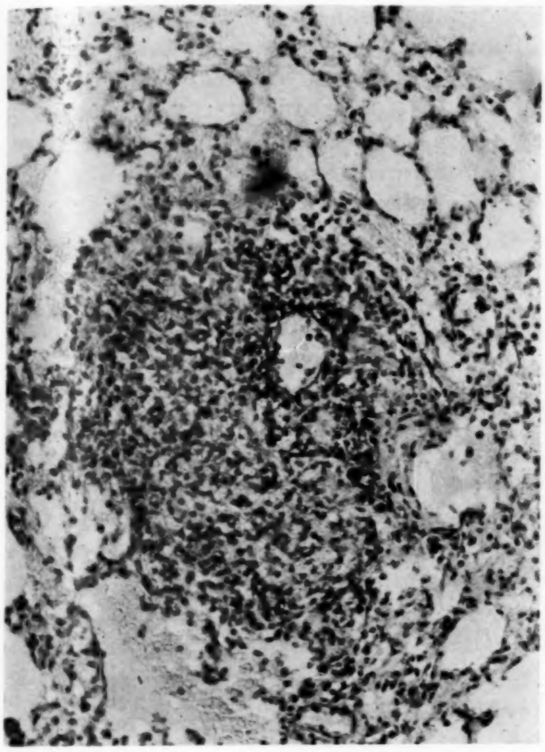

Fig. 8. A cross section of arteriolitis, showing the cuff-like arrangement of the infiltrate. Aldehyde-fuchsin and Van Gieson, ×180.

unknown and its significance in the further evolution of the lesions was not explored in these studies.

The arteriolitis found in these experiments might be due to three theoretical possibilities: pulmonary hypertension, hypersensitivity, and the effect of fibrin on the vascular wall. Although no direct measurements of pulmonary pressure were made in this study, the first possibility appears unlikely because of the following data: (1) In the animals receiving unilateral fibrin or whole blood clots (Groups A and E), arteriolitis was seen only in the embolized side. (2) In one animal in which arteriolar lesions were seen in both lungs (Dog No. 4 of Group E), proof was found that clotted blood emboli had passed to the opposite lung. (3) If there was pulmonary hypertension, it must have been low and/or transient, because the right side of the heart did not show dilatation or hypertrophy, and the blood vessels did not have lesions that could be attributed with certainty to hypertension, such as arterial medial hypertrophy or the presence of a muscular media in the arterioles[10-12]; furthermore, Jacques and Hyman[9] measured pulmonary arterial pressure in dogs which received 10 intravenous injections of blood clots, and found discrete and transitory elevations of pressure. (4) Finally, no vascular lesions were found in those dogs in which pulmonary circulation was obstructed by injections of plastic beads. For all these reasons it may be concluded that, if it ever existed, pulmonary hypertension did not represent a pathogenic factor in the production of arteriolitis.

Hypersensitivity is capable of producing acute inflammation of arteries and arterioles in many parts of the organism, including the lung. Two main reasons may be advanced in opposition to the idea that hypersensitivity could have played an important role in the production of arteritis as described in the present experiments. (1) Besides affecting arterioles, hypersensitivity also involves larger vessels that have a muscular media and produces necrosis and destruction of the wall; this was not found in the present material.

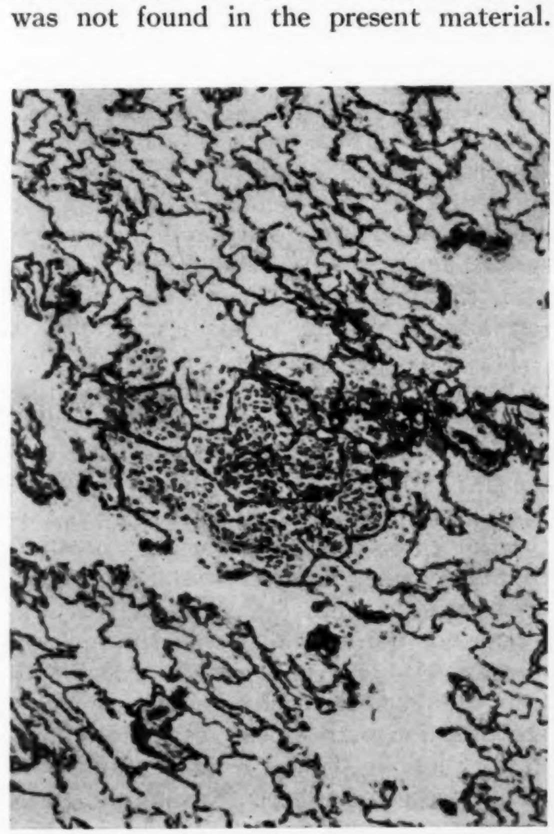

Fig. 9. The stroma of alveoli occupied by the inflammatory infiltrate of arteriolitis. Note the absence of vascular neoformation. Foot's stain, ×150.

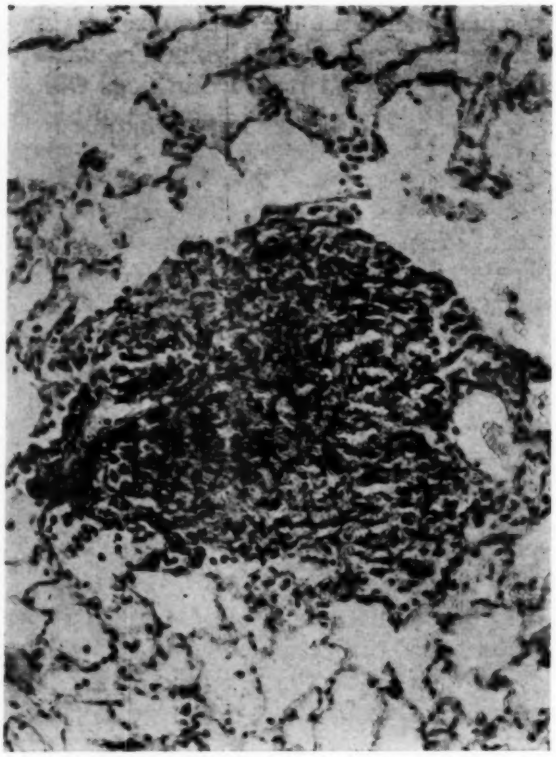

Fig. *10*. The integrity of the arteriolar wall in the area of inflammation can be demonstrated with elastic stains. Aldehyde-fuchsin and Van Gieson, ×180.

(2) Lesions were found 24 hours after embolization in those animals which had not received emboli previously, a finding which speaks against a hypersensitivity mechanism that requires a longer time for the formation of specific antibodies.

The data indicate that a factor residing in fibrin is responsible for the arteriolitis. Thus, the lesions appeared only in those animals with fibrin or whole blood embolism; arteriolitis was found only in vessels of the lung that had received this type of emboli. It must be kept in mind that acute arteriolitis was found away from organized thrombi, and that neither the lumen nor the arteriolar wall showed any alterations; furthermore, in animals which were sacrificed 24 to 72 hours after a single embolization with blood clots, the inflammatory lesions showed a larger number of well-preserved erythrocytes than did those in dogs examined 1 or 2 weeks after the last embolization. These data suggest that arteriolar damage is accompanied by an increase in arteriolar permeability with focal hemorrhage, and that the accumulation of inflammatory cells can be due, at least in part, to this hemorrhage. The fibrin factor responsible for arteriolitis would act only on those vessels in which it might have adequate concentration.

The preferential localization of arteriolitis at the sites of bifurcation of these vessels call to mind Arias-Stella's description[13] of the so-called "plexiform" or "angiomatoid" lesions found in primary pulmonary hypertension in man.[14] Evans[15] thought that capillary proliferation in the vicinity of an artery was due to a congenital defect in the elastica, but Arias-Stella showed by means of serial sections that the alteration is localized at the sites at which arteries give off much smaller vessels or arterioles. These studies have been confirmed by Wagenvoort.[16] The nature of the lesion herein described is different, however, since in this case foci of inflammatory cells are seen within the alveoli and around the arterioles, whereas in human primary pulmonary hypertension, "glomeruli" are formed by proliferation of capillaries within the arteriolar lumen.

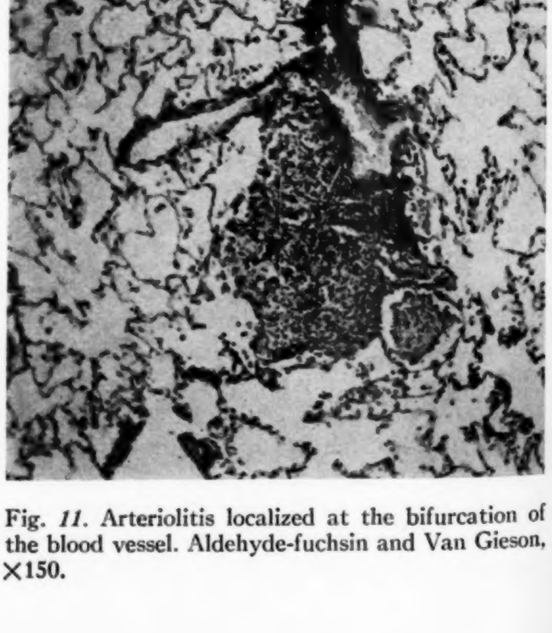

Fig. *11*. Arteriolitis localized at the bifurcation of the blood vessel. Aldehyde-fuchsin and Van Gieson, ×150.

This study was planned to aid in the interpretation of human pulmonary vascular lesions. If the findings in the dog can be extrapolated to human beings, then the results show that intimal thickening of arteries and arterioles, as well as arteriolitis, can be the consequence of embolism without the participation of hypertension or hypersensitivity. Therefore, even when functional and/or anatomic reasons would exist in a given case to assure the existence of pulmonary hypertension, the finding of lesions similar to those herein described suggests the need for a search for possible sources of emboli.

Summary

Numerous experimental studies have shown that it is possible to produce pulmonary vascular lesions by different methods. Two of the most effective methods are: (a) multiple embolization with blood clots, and (b) pulmonary hypertension produced by shunting systemic flow into the pulmonary artery or into one of its branches. Since many studies have failed to separate the effects of multiple emboli from those of pulmonary hypertension, a series of experiments were planned in which unilateral multiple pulmonary embolism was produced by injecting autologous fibrin clots in one group of animals, autologous whole blood clots in a second group, and plastic-bead emboli in a third group of dogs. Appropriate controls received the emboli through a peripheral vein, whereas the experimental animals were embolized through a catheter introduced into the left pulmonary artery. Another group of animals received a single embolization of whole blood clots into the left pulmonary artery and were sacrificed at intervals varying between 0 and 72 hours. The results were that in all animals which received fibrin or clotted blood emboli the three following types of pulmonary vascular lesions were found: (a) organized or partially organized clots in the lumen of arteries with minimal lesions in the wall, with the exception of, (b) a peculiar vacuolated aspect of the endothelium that was in intimate contact with the clots, and (c) peripheral arteriolitis without alteration in the arteriolar wall, accompanied by focal hemorrhage, usually localized at the branching sites of vessels. These lesions appeared 24 hours after the injection of emboli. No anatomic traces of pulmonary hypertension were found. No anatomic changes were seen in those instances in which plastic beads were given.

The results are discussed and it is pointed out that, whereas organized thrombi and endothelial vacuolation are due to the presence of the embolus, arteriolitis is probably the result of a fibrin factor. Pulmonary hypertension and hypersensitivity can be discarded as causal agents of the vascular lesions found in these experiments.

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Systolic I-J acceleration-force values of normal males from a Nickerson type of ultralow-frequency ballistocardiographic system

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In 1952, Jonnart[1] reported the use of a Nickerson type of platform for recording the ultralow-frequency[2] acceleration ballistocardiogram. Later, with associates,[3,4] the results of studies on 167 subjects were described. Particular emphasis was given to proposing a major theory relating the amplitude and time duration of the H-I-J waves to the degree of aortic elasticity or atherosclerosis instead of to the force (strength) of cardiac contraction or systolic stroke volume. Quantitative acceleration-force values were not given, and the Nickerson[5] type of modified system employed had a natural frequency of approximately 0.4 cycles per second.

In 1956, Hollis[6] reported preliminary results of quantitative acceleration-force studies from a small number of normal subjects, using the Nickerson[5] type of platform as one of three different ultralow-frequency systems under investigation. These acceleration-force studies were extended to a larger number of subjects, and results obtained from the pendulum[7] and ball-bearing[8] ultralow-frequency systems were reported in 1959. Similar studies for the Nickerson type of ultralow-frequency system constitute this report.

Although Starr[9] has recently demonstrated a very high correlation between the initial cardiac forces of systole and the H-I ejection-recoil stroke, most quantitative studies have been concerned with the systolic I-J stroke values. Accordingly, this report will be limited to the I-J stroke values from the Nickerson type of system and their comparison to published values from other ultralow-frequency systems.

Method

The system used has been described previously.[6] The platform had a natural frequency of 0.4 cycles per second, with a calculated response range from 0.2 c/s (F-1) to 9.6 c/s (F-2). The damping was obtained by a rod- "oil bellows" mechanism and was weak, i.e., 0.28 critical. The platform weighed 25,909 grams.

The transducer was a calibrated differentiating coil-magnet velocity meter.[10,11] The recorder was either a single-channel or double-channel Sanborn direct-writing electrocardiograph.

All subjects were found to be normal by cardiac auscultation, determination of blood pressure, and chest x-ray examination for cardiac size. Attainment of a basal state was not attempted, since prior observations had revealed deterioration of the ballistocardiogram with prolonged recumbency on the ballistic platform.

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*Table I. Data on subjects and platform, and acceleration and force values**

Subject, Age (yr.)		Height (cm.)	B.S.A. ($M.^2$)	Weight of subject (grams × 10^3)	Platform weight (grams × 10^3)	Subject + platform weight (grams × 10^3)	I-J_A-exp. (cm./sec.^{2})	I-J_A-exp. (force-grams)	I-J_A-insp. (cm./sec.^{2})	I-J_A-insp. (force-grams)
E.	(24)	168.9	1.68	60.000	25.909	85.909	3.21	281.59	4.5	394.76
D.B.	(23)	182.9	1.91	71.363	25.909	97.272	4.25	422.14	5.0	496.64
T.	(15)	174	1.78	66.136	25.909	92.045	5.18	486.87	5.73	538.57
L.C.	(31)	182.2	2.02	82.272	25.909	108.181	3.5	386.64	4.75	524.72
V.	(26)	195.6	2.37	106.818	25.909	132.727	3.0	406.59	3.5	474.36
D.L.	(24)	174	1.81	68.181	25.909	94.090	3.0	288.23	4.07	391.04
A.S.D.	(23)	174	1.80	67.272	25.909	93.181	3.25	309.24	4.25	404.39
E.T.	(24)	169	1.65	57.727	25.909	83.636	3.0	256.2	4.5	384.3
W.J.H.	(34)	165	1.54	50.909	25.909	76.818	2.7	211.79	3.3	258.86
J.A.R.	(25)	177	1.82	66.818	25.909	92.727	3.0	284.1	3.6	340.87
P.	(24)	172	2.08	96.818	25.909	122.727	2.7	338.37	3.0	375.96
L.P.	(22)	182	1.93	73.363	25.909	99.272	3.68	373.04	4.95	501.78
D.M.	(24)	180	2.03	85.000	25.909	110.909	2.4	271.8	2.7	305.78
R.C.	(31)	179	1.95	77.273	25.909	103.182	3.3	347.7	4.05	426.72
G.S.	(23)	173	1.84	71.818	25.909	97.727	2.7	269.44	3.45	344.28
R.T.	(24)	177.5	1.98	81.818	25.909	107.727	2.7	297.01	4.5	495.02
B.G.T.	(31)	170.6	1.82	72.045	25.909	97.954	3.9	390.09	4.8	480.12
J.C.F.	(24)	177.5	1.94	77.272	25.909	103.181	4.2	442.52	5.4	568.95
H.R.	(28)	185.4	2.05	79.091	25.909	105.000	4.25	455.68	6.24	669.04
A.D.M.	(29)	179	1.85	68.181	25.909	94.090	3.69	354.53	5.31	510.18
T.B.	(23)	169	1.68	60.454	25.909	86.363	5.74	506.2	7.04	620.85
C.	(25)	172.7	1.80	68.181	25.909	94.090	3.91	375.67	5.48	526.5
G.M.	(23)	182.9	1.82	63.636	25.909	89.545	4.0	365.75	5.8	530.3
Ra.	(22)	177.8	1.94	77.272	25.909	103.181	4.4	463.59	4.98	524.7
B.	(23)	180.3	2.02	84.091	25.909	110.000	2.14	240.37	3.43	385.27
Average	(25)	176.85	1.88	73.352	——	99.261	3.51	353.01	4.57	458.96
Standard deviation	(1) ±3.9	±6.56	±0.17	±12.177	——	±12.177	±0.86	±81.22	±1.07	±99.2

*Values of individual subjects with average and one standard deviation for all factors (excepting platform weight): age-years (average 25; standard deviation ± 3.9); height (176.85 cm.; ± 6.56); body surface area (1.88 sq. meters; ± 0.17); subject weight (73.352 Kg.; ± 12.177); subject plus platform weight (99.261 Kg.; ± 12.177). I-J expiration (3.51 cm./sec.^{2}; ± 0.86); I-J expiration force (353.01 grams; ± 81.22); I-J inspiration (4.57 cm./sec.^{2}; ± 1.07); I-J inspiration force (458.96 grams; ± 99.2).

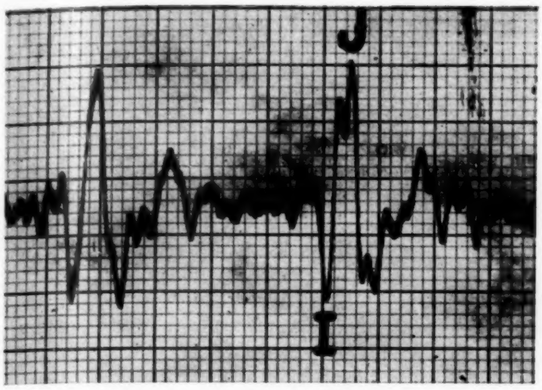

Fig. *1*. Acceleration record, suspended mid-respiration. Normal male subject, aged 25 years, weight 154 pounds, height 67.25 inches. Calibration: 14.0 small vertical spaces = 1.0 mv. = 3.0 cm./sec.^{2}; I-J wave = 21/14 × 3.0 = 4.5 cm./sec.^{2}.

Direct measurements of the I-J stroke acceleration value (calibration, 1.0 millivolt output = 3.0 cm./sec.^{2}) were made on expiratory and inspiratory records of a stable pattern from complex to complex. The force value was calculated for expiration and inspiration by the classic formula,

$$F = \frac{M \cdot A}{G}$$

with all measurements in the centimeter-gram-second system. The force (F) was in grams, the body plus platform mass (M) in grams, the acceleration (A) in cm./sec.^{2}, and the gravitational constant (G) for this geographic location[12] is 979.3 cm./sec.^{2}.

Complete data on subjects and platform, and acceleration (cm./sec.^{2}) and force (grams) values are given in Table I. An acceleration record (suspended mid-respiration) for a normal subject is shown in Fig. 1.

Discussion

Fig. 2 shows the frequency distribution of subject data, with one standard deviation, for age (*A*, years), height (*B*, centimeters), body surface area (*C*, square meters), and body plus platform weight (*D*, kilograms). Fig. 3 shows the frequency distribution, with one standard deviation, of the expiratory I-J acceleration (*A*, cm./sec.^{2}) and calculated force (*B*, grams) values, and the inspiratory I-J acceleration (*C*, cm./sec.^{2}) and calculated force (*D*, grams) values.

There are a few published values of quantitative acceleration measurements from ultralow-frequency systems to compare with values of this report. The mean I-J acceleration value given by Scarborough and associates[13] (25 male subjects, 20-29 years old) from a differential pendulum is 5.93 mg. Conversion (1.0 mg. = 0.98 cm./sec.^{2}) gives a value of 5.81 cm./sec.^{2}. Hollis obtained a mean I-J value of 5.01 cm./sec.^{2} from a simple pendulum[7] and 4.42 cm./sec.^{2} from a ball-bearing bed[8] ballistocardiograph.

The mean value (average expiration plus average inspiration I-J/2) of the present study with Nickerson type of spring ultralow-frequency system is 4.04 cm./sec.^{2}. This value is lower than the others because of the heavy platform (25,909 grams) of the Nickerson type of ultralow-frequency system.

It is of interest to compare these mean acceleration values with the theoretically predicted quantitative acceleration (force) value as determined by Noordergraaf and Heynekamp.[14] In Fig. 2 of their article[14] the amplitude of the I-J stroke is given in dynes. This value (280,000 dynes) may be converted to cm./sec.^{2} by division with the average total mass of body and ballistic platform (75,000 grams) as given by Noordergraaf and Heynekamp.[14] A resultant value of 3.73 cm./sec.^{2} is obtained. The closeness of this value to the experimentally determined values is quite good considering that the theoretical analysis of Noordergraaf and Heynekamp[14] is free of the mechanical factor of resonance amplification present in all ballistic systems.

Since the acceleration values given above are influenced by the mass of the ballistic platform, which increases inertial impedance to acceleration, a more exact comparison of these values would necessitate correction* for this factor. Use of the mean subject weight and the mean "subject plus platform" weight for each value given above results in the following corrected acceleration values: (1) Scarborough and associates,[13] differential pendulum, 6.33 cm./sec.^{2}; (2) Hollis,[7] simple pendulum,

*Corrected amplitude = measured amplitude times "body + platform" weight/body weight.

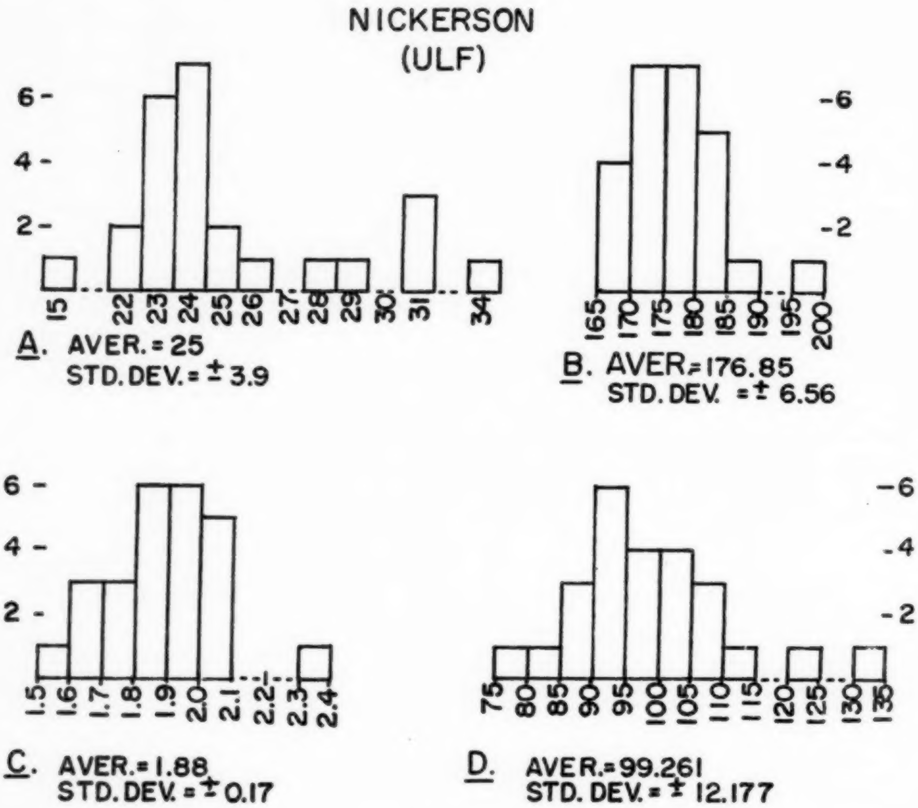

Fig. 2. Bar-frequency diagrams showing number of subjects with average and one standard deviation for: *A*, age in years; *B*, height in centimeters (group units of 5.0 cm.); *C*, body surface area in square meters (group units of 0.1 sq. meter); *D*, combined weight factor, body plus platform, in kilograms (group units of 5.0 kilograms).

6.00 cm./sec.^{2}; (3) Hollis,[8] ball-bearing bed, 5.29 cm./sec.^{2}; and (4) present study, 5.47 cm./sec.^{2}. These results show the best correlation between the differential pendulum and the simple pendulum, but all results are improved in reference to the differential pendulum. Correction of Noordergraaf and Heynekamp's[14] theoretical value, assuming a platform mass of 5,000 grams, gives 4.00 cm./sec.^{2} as the adjusted value. It is the least improved in reference to the differential pendulum, most likely due to the reason given previously, in addition to smallness of the assumed value for platform weight.

A similar comparison of mean force values of normal subjects from different systems is of interest. The mean force value from a differential pendulum[13] (25 male subjects, 20-29 years old) is 485.8 grams. Hollis has given a similar value of 435.24 grams from a simple pendulum[7] and 397.38 grams from a ball-bearing bed[8] ballistocardiograph. The mean force value (average expiration plus average inspiration I-J/2) of the present study is 405.99 grams. An average value determined from data given by Von Wittern[15] (4 subjects, simple pendulum) is 365 grams. Conversion of the theoretical force value (280,000 dynes) of Noordergraaf and Heynekamp[14] gives a value of 285.7 grams. The lowness of this last value is likely due to factors already mentioned in a discussion of the acceleration values. Calculation of the "true" unloaded force value by multiplying the corrected mean acceleration value by the mean subject weight for each system did not result in any significant improvement, except for the value from the simple pendulum used by Hollis,[7] i.e., an increase of 14.3 grams. The lack of improvement in corrected values is explained by the greater mass (subject plus platform) used when calculating force from the uncorrected, directly measured platform acceleration.

Although not strictly comparable because of differences in characteristics of

the systems, it is of interest to note the force value obtained for normal subjects from a spring type of high-frequency platform. Starr[16] obtained a mean (expiration plus inspiration/2) value of 413 grams (range, 406-420) for healthy young male adults. This is a reasonably good agreement with the force values obtained by the ultralow-frequency technique. An average value obtained from the five mean ultralow-frequency values given previously is 417.88 grams. The closeness of this average value to Starr's[16] high-frequency-platform value is significant.

At present it would appear, as has been stated,[7] that the differential pendulum[13] is the most efficient system to date for obtaining the acceleration-force values of the ultralow-frequency ballistocardiogram.

Summary

1. The acceleration-force values of 25 normal male subjects from a Nickerson type of ultralow-frequency ballistocardiographic system have been given.

2. The resultant mean values have been compared to values from other ultralow-frequency systems, and theoretically corrected acceleration values have been calculated for each system.

3. The force value for normal subjects from a spring type of high-frequency system has been compared to an average mean value obtained from force data of five ex-

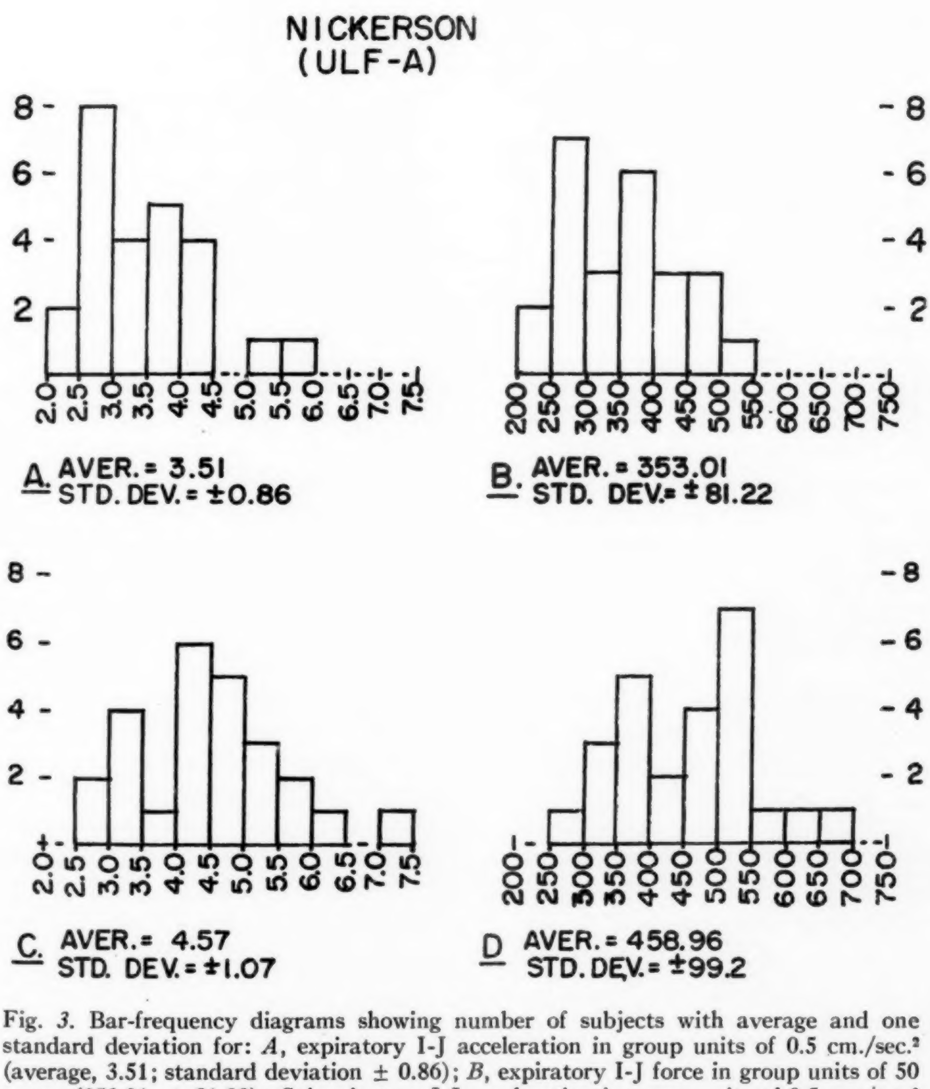

Fig. 3. Bar-frequency diagrams showing number of subjects with average and one standard deviation for: *A*, expiratory I-J acceleration in group units of 0.5 cm./sec.^{2} (average, 3.51; standard deviation ± 0.86); *B*, expiratory I-J force in group units of 50 grams (353.01; ± 81.22); *C*, inspiratory I-J acceleration in group units of 0.5 cm./sec.^{2} (4 57; ± 1.07); and *D*, inspiratory I-J force in group units of 50 grams (458.96; ± 99.2).

perimental studies using the ultralow-frequency technique. The closeness of the two values is remarkable.

4. It appears that the most efficient and sensitive of the ultralow-frequency systems is the differential pendulum.

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Cardiovascular and antiarrhythmic activity of amotriphene

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Recent clinical and experimental studies have indicated that amotriphene* possesses interesting and important therapeutic properties for the treatment of angina pectoris and mild cardiac arrhythmias. Karczmar, Bourgault and Elpern[1] have reported a significant cardiac antiaccelerator activity in the epinephrine-driven rabbit heart and an in vitro coronary dilator activity two to three times that of papaverine. Bobb and Green[2] have reported significant in vivo coronary dilator activity in the dog, and Farah and Birnbaum[3] have reported antiarrhythmic properties in the isolated rabbit auricles and in the intact dog that were approximately 4 and 8 times as effective as those of quinidine and Pronestyl, respectively. Page and Sasse[4] have reported an increase in coronary sinus oxygen saturation in dogs. Introductory clinical studies by Harris[5] indicate that this drug is effective in the treatment of angina as well as cardiac arrhythmias of both atrial and ventricular origin. The present study is a report of further laboratory studies on the cardiovascular activity and toxicity of this compound.

Methods

Experimental studies were conducted under a variety of procedures. The basic experimental technique used dogs anesthetized with pentobarbital, 30 mg./Kg. intravenously, and maintained on artificial respiration with room air. Arterial blood pressure was measured with a Statham transducer from the femoral artery. Heart contractile force was measured with a Walton strain gauge attached to the surface of the right ventricle. Both parameters were recorded with a Grass oscillograph. Electrocardiograms (ECG—Lead II) were taken throughout the experiments. In some instances the other bipolar and unipolar leads were also recorded. Amotriphene was administered intravenously into the femoral vein.

Experiments in 19 dogs were carried out by means of this procedure. Eleven other experiments were conducted in dogs pretreated with morphine, 10 mg./Kg. subcutaneously, and pentobarbital, 15 mg./Kg. intravenously, followed by penthienate bromide, 0.5 mg./Kg. subcutaneously. The latter drug, a parasympatholytic, produces

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*Myordil, 3-dimethylamino-1,1,2-tris-(4-methoxyphenyl)-1-propene hydrochloride, (WIN 5494) registered trade mark, available from Winthrop Laboratories, Inc., New York, N. Y.

a sustained sinus tachycardia within 15 minutes after administration.

Eighteen experiments were conducted in dogs administered sublethal doses of digitalis, using ouabain, digitoxin U.S.P., or digitalis tincture U.S.P. Each digitalis preparation was administered intravenously in divided doses or by slow continuous infusion in an amount equaling an ultimate dosage of 0.5 to 1.02 cat units per kilogram, equivalent to milligram units previously published.[6] The establishment of a ventricular ectopic tachycardia, single or multifocal, of at least 10 minutes' duration was the criterion of digitalis toxicity. Amotriphene was administered intravenously in increments of 2.0 mg./Kg. at 5-minute intervals until the arrhythmia was converted to a normal sinus rhythm or until heart block occurred.

Two experiments were conducted in chemically sympathectomized dogs, using the procedure of Brewster, Bunker and Beecher.[7]

ECG toxicity studies were conducted in 26 cats, using the U.S.P. digitalis assay method to determine the interrelationship of amotriphene and digitalis toxicity. Studies were also conducted in 7 dogs and 7 monkeys administered amotriphene orally by stomach tube at doses of 10.0 to 25.0 mg./Kg. for periods ranging from 3 days to 12 months. Four dogs were titrated to death with continuous intravenous infusion of amotriphene.

The in vitro cardiac activity of amotriphene was determined in isolated rabbit hearts by means of a modified Langendorf perfusion technique. Inotropic changes were measured with a Grass FT .03 force displacement transducer. Amotriphene was administered at log dose intervals of 25 to 200 micrograms per heart, using 3 hearts and 3 injections of drug per heart for the determination of each point.

Results

The response of intravenously administered amotriphene on heart rate, blood pressure, and heart contractile force in dogs is shown in Table I. There was a decrease in heart rate, systolic and diastolic blood pressure, and an apparent moderate increase in heart contractile force. The decrease in arterial pressure and the positive inotropic response were of relatively short duration (5 to 20 minutes), whereas the negative chronotropic response was considerably longer (20 to 90 minutes). There were no changes in the ECG at the lower doses. Doses of 8.0 and 16.0 mg./Kg. produced increasing changes in the ECG pattern, consisting of an increase in the refractory period as measured by an increase in the corrected Q-T interval, and a slight increase in conduction time as measured by an increase in the QRS interval.

The action of amotriphene on sinus tachycardia induced by penthienate bromide is shown in Table II. Within the dosage range used there was a marked inhibition of the sinus tachycardia. The duration of this negative chronotropic action ranged from 30 to 90 minutes.

The results of the study of the action of amotriphene on digitalis toxicity are contained in Table III. Of the total of 18 experimentally induced digitalis arrhythmias, there were 12 complete reversions to normal sinus rhythm with amotriphene. There were 5 partial reversions, of which 3 resulted in partial heart block, and there was 1 unsuccessful attempt at reversion. The total dosage for reversion varied from 2.0 to 18.0 mg./Kg., and the duration of complete reversion, after the final administration of amotriphene, ranged from 1 to 6 hours. It should be recognized that this is a relatively short period of observation for this type of experiment, and it is possible that, had the experiments been followed for periods up to 12 hours, there might have been some instances of reversion to a ventricular ectopic rhythm, since it is anticipated that the duration of action of amotriphene is shorter than that of digitalis. These experiments, however, do demonstrate the ability of amotriphene to bring about the conversion of a digitalis-induced arrhythmia.

The results of experiments conducted in cats, using the U.S.P. digitalis assay method, are contained in Table IV. Within the limits of these experiments, amotriphene did not raise the lethal dose of digitalis. Various other dosage schedules of amotriphene not contained in Table IV were also carried out but were unsuccessful. In no instance were we able to significantly raise the lethal dose of digitalis. We were

also unable to demonstrate any increased toxicity for the combination of amotriphene and digitalis within the limits of these experiments.

The results of ECG studies in dogs and monkeys are summarized below. Two dogs which received 10 mg./Kg. of amotriphene orally for 21 days developed no cardiac arrhythmias, there was little change in heart rate, and there were no changes in the refractory period or conduction time. Five dogs which received 20 mg./Kg. of amotriphene for varying periods of medication up to 18 days had essentially the same ECG pattern as those which received 10 mg./Kg. There were no cardiac arrhythmias, changes in conduction time, or refractory period. Dogs which received the 20-mg. dose did exhibit stimulation of the central nervous system. In 2 animals this stimulation was sufficient to be fatal within 3 days after the start of drug therapy.

The ECG pattern of activity for the 4 dogs titrated to death with amotriphene was similar for each animal. This consisted of gradually increasing voltages in the S and T waves, moderate changes in the P and R waves, increased refractory period and conduction time, and increased activity of the central nervous system which resulted in overt seizures and convulsions. After the onset of marked stimulation of

Table I. *Cardiovascular changes induced by intravenous amotriphene in anesthetized dogs*

Dose	Heart rate		Blood pressure		Heart contractile force
	Control ± S.E. (beats/min.)	*% Decrease*	*Control ± S.E. (mm. Hg)*	*% Decrease in mean pressure*	*(% Increase ± S.E.)*
2 mg./Kg.	177.4 ± 10.5	16.5	134.3 ± 6.7 / 100.7 ± 3.9	28.6	20.5 ± 4.5
4 mg./Kg.	136.0 ± 26.4	21.5	103.3 ± 21.4 / 73.3 ± 15.3	33.7	18.6 ± 5.1
8 mg./Kg.	96.0 ± 9.24	30.0	127.1 ± 8.5 / 73.6 ± 9.6	38.4	20.1 ± 6.8
16 mg./Kg.	151.5 ± 9.4	43.5	113.1 ± 9.9 / 80.0 ± 6.7	46.1	21.8 ± 8.3

Table II. *Action of amotriphene in anesthetized dogs with tachycardia induced by penthienate bromide*

Dose	Heart rate		Blood pressure		Heart contractile force
	Control ± S.E. (beats/min.)	*% Decrease*	*Control ± S.E. (mm. Hg)*	*% Decrease in mean pressure*	*(% Increase ± S.E.)*
1 mg./Kg.	228.0 ± 13.8	16.2	146.3 ± 16.5 / 112.5 ± 16.6	14.8	19.0 ± 5.6
2 mg./Kg.	193.7 ± 10.4	25.3	149.3 ± 7.1 / 113.6 ± 6.8	24.7	15.3 ± 6.1
4 mg./Kg.	222.0 ± 6.8	48.2	148.3 ± 12.2 / 99.2 ± 11.2	28.9	22.2 ± 7.9

Table III. *Action of amotriphene on cardiac arrhythmias of digitalis toxicity in anesthetized dogs*

Experiment number	*Glycoside and dose (cat unit/Kg.)*	*Dose needed for reversion (in multiples of 2 mg./Kg.)*	*Additional injections*	*Total dosage (mg./Kg.)*	*Time of final ECG (hours)*
1.	Ouabain 0.5	1	2	6.0	1.3
2.	Ouabain 0.5	2	1	6.0	1.0
3.	Ouabain 0.5	3	0	6.0	1.2
4.	Ouabain 1.0	Not reverted	7	14.0	1.0
5.	Ouabain 0.5	2	2	8.0	1.5
6.	Ouabain 0.5	1	0	2.0	2.0
7.	Ouabain 0.5	5	0	10.0	3.8
8.	Ouabain 0.5	2	0	4.0	2.0
9.	Ouabain 0.75	2	2	8.0	3.0
10.	Ouabain 0.5	5	4	18.0	2.5
11.	Tincture 0.6	4. Incomplete, partial heart block	0	8.0	4.2
12.	Tincture 0.75	2. Incomplete, partial heart block	0	4.0	2.5
13.	Tincture 1.2	3	1	8.0	4.5
14.	Tincture 0.6	2	1	6.0	3.2
15.	Tincture 0.75	1. Incomplete, partial heart block	0	2.0	1.0
16.	Digitoxin 0.83	2. Partial, occasional runs of ectopic beats	0	4.0	2.5
17.	Digitoxin 0.75	3. Partial, occasional runs of ectopic beats	0	6.0	1.5
18.	Digitoxin 0.50	1	0	2.0	6.0

Table IV. *Comparison of digitalis assay in cats and amotriphene activity*

Drug	*Dose (mg./Kg./5 min.)*	*Number of animals*	*Lethal dose (mg./Kg. ± S.E.)*
Ouabain	0.005	5	0.115 ± 0.0019
Ouabain	0.0075	5	0.1095 ± 0.0038
Amotriphene	2.0	8	61.8 ± 7.0
Ouabain and amotriphene	0.0075 2.0	8	0.1012 ± 0.004

the central nervous system there were increasing periods of ventricular ectopic beats, heart block, runs of ventricular ectopic tachycardia, complete A-V dissociation, and eventually respiratory embarrassment coincident with a decerebrate rigidity and finally ventricular fibrillation. Final lethal doses of amotriphene ranged from 21 to 127 mg./Kg.

The 2 monkeys which received 12.5 mg./Kg. per day orally of amotriphene developed no cardiac arrhythmias, changes in refractory period, or conduction time. The only change observed was a slight increase in the voltage of the S and T waves.

The 5 monkeys treated with 25 mg./Kg. per day orally of amotriphene all exhibited the same pattern of ECG activity. This included moderate bradycardia, an increase in refractory period of 10 to 15 per cent, and an occasional increase in conduction time. Each animal developed moderate drug-induced arrhythmias of short duration. These were never consistent for the same animal. The arrhythmias developed approximately 2 hours after administration of the drug, and in almost all instances reverted to a normal sinus rhythm by 6 to 8 hours after administration of the drug. Changes consisted of partial heart block, occasional ventricular extrasystoles, and nodal rhythms. The T and S waves developed increased voltages, whereas the P and R waves remained unchanged.

The results of studies in isolated rabbit hearts demonstrated that amotriphene produced a small to moderate negative inotropic action on the myocardium. These results are shown in Table V. Earlier studies in intact dogs, using the Walton strain gauge, had shown amotriphene to have an apparent positive inotropic action. The 2 experiments conducted in sympathectomized dogs demonstrated that intrave-

nously administered amotriphene produced a positive inotropic response before sympathetic block and a negative inotropic response after sympathetic block. It is probable, therefore, that the moderate positive inotropic response seen in the initial dog preparation was not due to direct cardiac stimulation of amotriphene, but was probably due instead to reflex sympathetic cardiac stimulation initiated by the hypotension after administration of amotriphene.

Discussion

A unique combination of properties makes amotriphene an interesting therapeutic drug; it is a coronary dilator,[1,2] has the ability to increase coronary sinus oxygen saturation,[4] is devoid of cardiac stimulating action, produces moderate bradycardia, and possesses antiarrhythmic properties.

Farah and Birnbaum[3] have reported amotriphene to be 4 and 8 times as effective as quinidine and Pronestyl, respectively, in increasing the refractory period of the isolated rabbit atrium and equal to quinidine in decreasing conduction velocity. They have also demonstrated the ability of amotriphene to produce a reduction in the auricular and ventricular rate of auricular flutter and fibrillation, and to produce reversion to a normal sinus rhythm. The present studies have demonstrated the ability of amotriphene to revert the arrhythmias of digitalis toxicity to normal sinus rhythm. Thus, there appears to be no contraindication for the concurrent use of digitalis and amotriphene. One may also surmise that amotriphene may play an important part in bringing about relief for the anginal patient who exhibits disturbances of rhythm, since anginal pain has been reported by many investigators to be relieved after the abolishment of rhythm disturbances of many varieties and the re-establishment of a normal sinus rhythm.

Table V. ***Amotriphene-induced changes in heart contractile force in the isolated rabbit heart***

Dose (micrograms/heart)	*% Decrease in heart force*
25	3.4
50	4.8
100	12.6
200	15.3

The coronary dilator activity of amotriphene suggests that the drug may be effective in conditions of myocardial anoxia. Papaverine is moderately effective as a relaxant of smooth muscle and coronary dilator. Unfortunately, though, it is effective in only a small percentage of clinical situations, and this may be due to the fact that it stimulates the myocardium to a proportionately greater extent than it increases coronary blood flow. Bobb and Green[2] have shown that amotriphene produces not only a greater mean coronary blood flow but also increases both the systolic and diastolic portions of coronary flow, and at the same time causes no increase in myocardial contractility or change in the duration of systole. They have also demonstrated that amotriphene is similar in activity to, but more potent than, sodium nitrite.

Recently, Darby and Aldinger[8] have studied the cardiac pharmacology of nitroglycerin, and have suggested that nitroglycerin may achieve its therapeutic efficacy through its ability to decrease the peripheral work load on the heart as well as its ability to increase coronary flow. In addition, and perhaps more importantly, they suggest that nitroglycerin may participate in the metabolism of the cardiac contractile mechanism in such a way as to increase its efficiency. Preliminary studies by this group indicate that amotriphene has a pattern of activity similar to that of nitroglycerin (personal communication from Darby). The moderate bradycardic action of amotriphene on the normal heart rate, the slight decrease it produces in blood pressure, and its slight negative inotropic action in the experimental animal all lend substance to the premise that this drug may reduce the peripheral work load of the compromised, hypoxic heart. This property is in addition to its ability to dilate the coronary vascular bed and to increase coronary sinus oxygen saturation. In patients with marked sinus tachycardia, amotriphene would be expected to produce a greater degree of bradycardia than in the patient with a normal heart rate. In both

the epinephrine-driven heart[1] and the sinus tachycardia induced by a parasympatholytic drug as reported in this study, amotriphene has demonstrated an ability to bring about a moderate to marked decrease in heart rate.

The cardiovascular toxicity studies conducted in dogs and monkeys indicate that high doses of amotriphene are more neurotoxic for the dog than for the monkey. In fact, stilbenes in general, to which amotriphene is related chemically, are known to be particularly toxic to the dog, as compared to man and other animals.[9] However, as with any drug that acts upon the conducting system of the heart to diminish automaticity, amotriphene, particularly in high doses, may bring about disturbances in cardiac rhythm. In man, the level of drug needed to produce these effects probably exceeds by many fold the recommended therapeutic dosage level. In those instances in which disturbances in rhythm do occur, animal studies indicate that withdrawal of the drug brings about rapid reversal to a normal sinus rhythm.

A recent report by Sandler[10] indicates that amotriphene was not significantly superior to a placebo in the relief of angina pectoris in 13 patients, using a double-blind technique. Patients in this study were given amotriphene in a dose of 25 mg. four times daily. Recent unpublished clinical observations indicate that higher doses of amotriphene may be needed to produce significant relief in anginal-like conditions. The studies of Harris,[5] however, indicate significant relief in anginal patients as indicated by increased work capacity and reduced requirements for nitroglycerin. In addition, Harris reported significant relief for patients with cardiac arrhythmias of both atrial and ventricular origin. The experimental studies completed to date suggest an important pattern of activity that should be clinically useful.

Summary

Amotriphene (Myordil, WIN 5494) has been shown to have a coronary dilator activity about twice that of papaverine, yet to be devoid of myocardial stimulant action. Amotriphene will significantly reduce the sinus tachycardia induced by a parasympatholytic drug, and will reduce to a lesser extent heart rates in normal animals. Amotriphene is 4 and 8 times more active than quinidine and procaine amide, respectively, in increasing the refractory period of the isolated rabbit atrium. It is equal to quinidine in decreasing conduction velocity. It will reduce auricular and ventricular rate as well as produce normal sinus rhythm in experimentally induced auricular flutter and fibrillation. Amotriphene will convert digitalis-induced cardiac arrhythmias to a normal rate. This combination of coronary dilator and cardiac antiarrhythmic properties of amotriphene is of potential value in the treatment of angina-like conditions and the milder cardiac arrhythmias.

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Experimental study on the intramural distribution of the excitability cycle and on the form of the epicardial T wave in the dog heart in situ

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Although the spread of excitation through the ventricular wall has been studied extensively during recent years, little information is available about the spatial distribution of the repolarizing process. Because repolarization occurs much more slowly than depolarization, it cannot be investigated adequately with the available extracellular recording methods, which are applied to the study of excitation. For technical reasons it has not yet been possible to investigate the electrical systole in its entire length in all layers of the ventricular wall by means of intracellular or suction electrodes. Therefore, only indirect methods can be used for this purpose, of which determination of the excitability cycle has been applied already by Wilson and Herrmann,[1] in their studies on the ventricular gradient.

Recent studies by Hoffman and Cranefield[2] justify this approach, since they demonstrated that in normal conditions the time course of the threshold has a constant relation to the time course of the membrane action potential.

In some studies[3,4] the differences in the time of duration of the electrical systole in the endocardial and in the epicardial layers were determined. Such determinations do not necessarily indicate the temporal sequence of repolarization across the ventricular wall.

The technique which employs needle electrodes[5] makes possible the analysis of the excitability cycle at all levels within the ventricular wall.

The present study was undertaken in order to determine the temporal relations of the recovery process at different depths of the left ventricular wall and to correlate these findings with the polarity of the T wave in epicardial leads.

Methods

Eight mongrel dogs were used, anesthetized with a long-acting barbiturate. After intubation, respiration was maintained by a pump. The heart was exposed by a lateral thoracotomy and suspended in a pericardial cradle. Care was taken to prevent cooling and drying of the exposed heart by application of cotton wool soaked in warm saline, and by closing the thorax thoroughly as soon as possible.

By means of a D.C.-operated heating blanket wrapped around the animal the intrathoracic temperature was maintained at 37°C. The heart was driven at a constant rate by square wave pulses delivered by an independent stimulator to a bipolar electrode stitched onto the left auricle.

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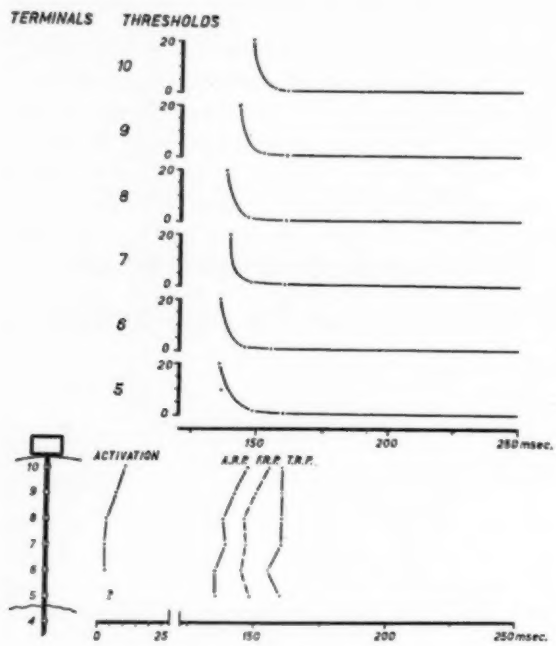

Fig. *1. Upper part:* Strength/interval curves for unipolar cathodal stimulation, for all terminals of a needle electrode, situated in the left ventricular wall of a dog's heart in situ. Thresholds determined at intervals of 5 msec. in the cardiac cycles. *Horizontal:* Intervals in the local excitability cycle. *Vertical:* Thresholds in multiples of the diastolic level. Dots indicate the end of the A.R.P., F.R.P., and T.R.P. Duration of testing pulses: 0.5 msec. *Lower part:* Diagram of the temporal relations during activation and recovery of excitability. *Horizontal:* Intervals in the local excitability cycle. *Vertical:* Terminals of the needle electrode. Experiment of Sept. 6, 1956. Discussion in text.

Testing pulses were delivered to the terminals of a needle electrode[5] inserted into the mid-anterolateral portion of the left ventricle. All intervals in the cardiac cycle were measured in respect to the time of occurrence of the intrinsic deflection in a unipolar lead from a terminal of a second needle electrode inserted as close as possible to the needle used for stimulation. For this purpose this lead was fed into a synchronizer, starting the variable delay circuit of the testing stimulator. The excitability cycles of the different layers were analyzed by determining at every 5-millisecond interval the threshold for unipolar cathodal stimulation at each successive separate intramural terminal of the stimulating electrode. All stimuli were separated from earth, without appreciable distortion, by means of special 1:1 transformers. For recording and stimulating purposes, indifferent electrodes were placed subcutaneously on the extremities.

In some experiments, cooling or heating of the epicardial surface was effected by applying, without exerting appreciable pressure, a pliable thin-walled rubber tube on the epicardial surface around the head of the stimulating needle electrode. Through this tube, water of 45°, respectively 20°C., was circulated for a short time, while a new series of threshold determinations was carried out.

At every terminal the time of arrival of the excitatory wave was determined from the intrinsic deflection in unipolar leads, and measured in regard to the intrinsic deflection in the reference lead. In addition, the following measurements were made from the strength/interval curves obtained: (1) the end of the *absolute refractory period* (A.R.P.), as defined arbitrarily by the threshold reaching the 20-fold of the diastolic level[6]; (2) the end of the *functional refractory period* (F.R.P.), as defined by the threshold reaching the 1.5-fold of the diastolic level, according to our findings described elsewhere[7]; (3) the end of the *total refractory period* (T.R.P.), as defined by the threshold reaching the diastolic level.

Results

A. Transmural sequence of recovery. The strength/interval curves for cathodal stimuli determined at the successive intramural terminals generally have the same contour (Figs. 1-3, *upper part*). Slight differences were caused by the temporal sequence of activation across the ventricular wall and by local variations in the duration of the refractory state.

The progress of recovery through the ventricular wall can be studied from the sequence of the end of different refractory periods. In our opinion the best available index of the restoration of excitability is the end of the F.R.P., since this marks the restoration of an essential property of myocardial tissue: the conduction of the excitatory wave.

Furthermore, this point can be measured accurately from the strength/interval curves. In contrast, the end of the T.R.P. can only be estimated with an error of approximately 5-10 milliseconds, because during this part of the cardiac cycle the thresh-

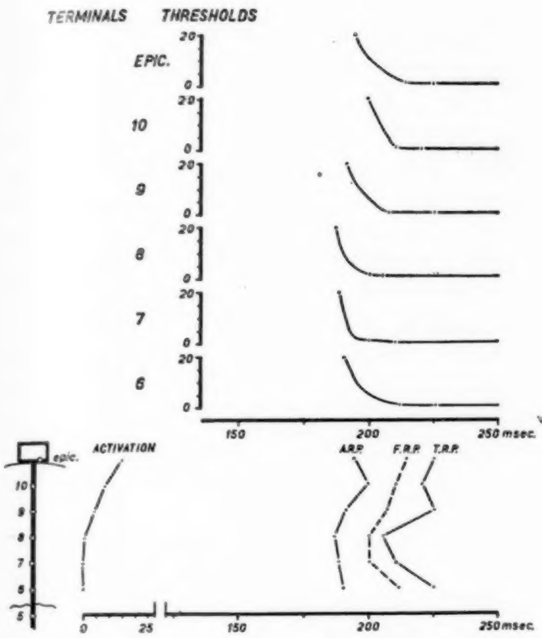

Fig. *2*. Same explanation as for Fig. 1. Experiment of April 14, 1956. Discussion in text.

old declines rather gradually. As can be seen from Figs. 1-3 (*lower part*), the course of the end of the T.R.P. in the successive intramural layers sometimes is rather erratic and does not follow the same sequence as that of the end of the A.R.P. and F.R.P. in these layers. The end of the A.R.P., as defined above, can be determined without any appreciable error, but its functional significance is dubious. During heating and cooling of the epicardial surface, however, we sometimes had to resort to this accurately and quickly to determine mark-point, even if this introduces a slight error (Fig. 4). The rapidity of the changes in the duration of the electrical systole prevented the determination of complete strength/interval curves for all terminals.

In these experiments the functional recovery follows rather closely the same time course as the spread of activation through the middle and outer part of the ventricular wall. In these layers the duration of the F.R.P. is nearly equal. In the innermost layer, however, the F.R.P. sometimes is approximately 15 milliseconds longer than in the middle and subepicardial layers.

These results show convincingly that recovery does not spread across the ventricular wall in a linear way, and that predictions from determinations of the time course of excitability carried out at the endocardial and epicardial surfaces are erroneous. The middle layers may show large deviations from such a linear spread because recovery may occur relatively early.

B. Heating and cooling of the epicardial surface. In all control observations the the T wave was negative in unipolar leads from the epicardial surface near to the needle electrode. In the experiment with a negative epicardial T wave, illustrated in Fig. 5, the end of the F.R.P. in the layers just beneath the epicardial
later
surface occurred approximately some 10 milliseconds earlier than in the subendocardial layers. The negative epicardial T wave may be explained by a later repolarization in the middle and outer layers of the ventricular wall.

During cooling of the epicardial surface the absolute refractory period is increased throughout the whole diameter of the

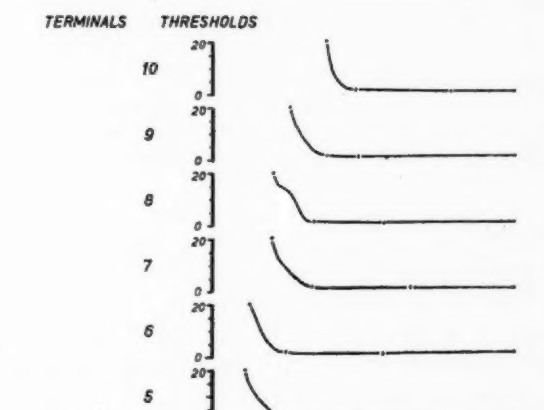

Fig. *3*. Same explanation as for Fig. 1. Experiment of Feb. 1, 1956. Discussion in text.

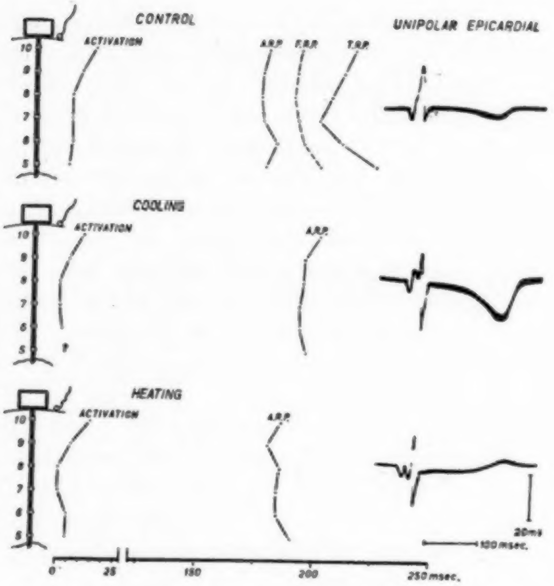

Fig. *4*. Temporal relations between activation and recovery of excitability for unipolar cathodal stimulation at all terminals of a needle electrode which are situated in the left ventricular wall of a dog's heart in situ, together with unipolar electrogram from epicardial terminal. End of A.R.P., F.R.P., and T.R.P. taken from complete strength/interval curves. Duration of testing pulses is 0.5 msec. *Upper part:* Control. *Middle part:* During cooling of epicardial surface. *Lower part:* During heating of epicardial surface. Experiment of March 22, 1956. Discussion in text.

ventricular wall, and a deep negative T wave is recorded from the epicardium. The observed small differences in time of recovery between the individual layers do not predict such a large change in the voltage of the T wave.

During heating of the epicardial surface a positive epicardial T wave is observed. The A.R.P. is now shortened throughout the ventricular wall. The differences in time between the end of the refractory period in the different layers are rather small, although consistent with the T-wave changes, according to the concept of the ventricular gradient.

These observations led us to suppose that a change in the transmural sequence of restoration of the excitability was not the sole factor associated with the marked changes in the polarity of the epicardial T wave, as has been postulated by Nahum and Hoff.[8]

In some experiments the time relations in the restoration of excitability between this section of the ventricular wall and more distant parts of the ventricle were analyzed. Fig. 5 illustrates a typical experiment. In this experiment, four needle electrodes were inserted into the anterolateral part of the left ventricular wall. Three were placed, respectively, at the apex, near to the coronary sulcus, and close to the anterior septal part of the left ventricle. Within the triangle formed by these three needle electrodes a fourth needle electrode was inserted (Fig. 6, *inset*); the distance between it and the others was approximately 3-4 cm. The head of this needle carried two electrodes in contact with the epicardial surface: one of these was used for stimulation, the other for recording.

In the control observations, at the epicardial terminal of the central electrode, all refractory periods were completed later than in the corresponding layers at the other needle electrodes (Fig. 6, *upper part*). The sequence of the completion of the A.R.P., F.R.P., and T.R.P. in this part of the wall indicates that recovery occurred later in the outer parts of the wall. This should lead one to expect a negative T deflection at the epicardial surface, which indeed was observed.

During heating of the epicardial surface the epicardial T wave became positive, and the duration of all refractory periods was shortened (see Fig. 5). The A.R.P. of the outer layers is now shorter than in the inner layers, and a positive T wave is expected. The completion of the F.R.P. occurs nearly synchronously in inner and outer layers, but there is a large difference between the muscle layer in contact with terminal 11, at the epicardial surface, and that near to terminal 10. The larger duration of the F.R.P. at the latter terminal should lead one also to expect a positive T wave. The sequence of the end of the T.R.P., however, is such that a negative T deflection from the epicardial surface should be expected.

If one compares the duration of the refractory periods determined at the central terminal with those at the other terminals, important differences in time are seen (Fig. 6). During the control observations these differences indicate that repolarization occurs later at the central electrode, and there a negative epicardial T wave is

observed. Heating of the epicardial surface causes a diminution of all three refractory periods in the heated area, which is now repolarized earlier than the surrounding parts. The epicardial T wave is positive.

Discussion

From these observations the conclusion can be drawn that the functional recovery of the myocardium follows a regular sequence across the ventricular wall. Nowhere did we find evidence of an erratic progress of the end of the functional refractory period. This indicates that an extrasystole, arising after the end of the functional refractory period, will be conducted in a homogeneous way and will meet no refractory tissue on its way, when spreading in a direction perpendicular to the epicardial surface.

It has been assumed that the sequence of repolarization across the ventricular wall can be deduced by interpolation of the determinations of the end of the electrical systole made on the endocardial and epicardial sides only.[3,4]

However, it follows from our experiments that this assumption is not justified. Large deviations may be present from a linear progress of recovery in the interposed muscle layers. In the middle layers, recovery may be more advanced than in the inner and outer layers. This implies that the polarity of the epicardial T wave cannot be explained only on a basis of the difference in time of repolarization in inner and outer layers. This view has been expressed before by Hoff and Nahum.[9] We found it impossible in most cases to predict the polarity of the epicardial T wave from the temporal sequence of the completion of the A.R.P., F.R.P. and T.R.P. through the different layers of the ventricular wall. We feel that the method of determining the duration of the refractory periods across the ventricular wall does not give satisfactory information for this purpose.

At least two other factors contribute to the polarity of the epicardial T wave. Our findings demonstrate that, also, differences in time in the completion of recovery between the area near the recording electrode and the adjacent areas have to be considered.

Furthermore, we observed occasionally that at the beginning of heating of the

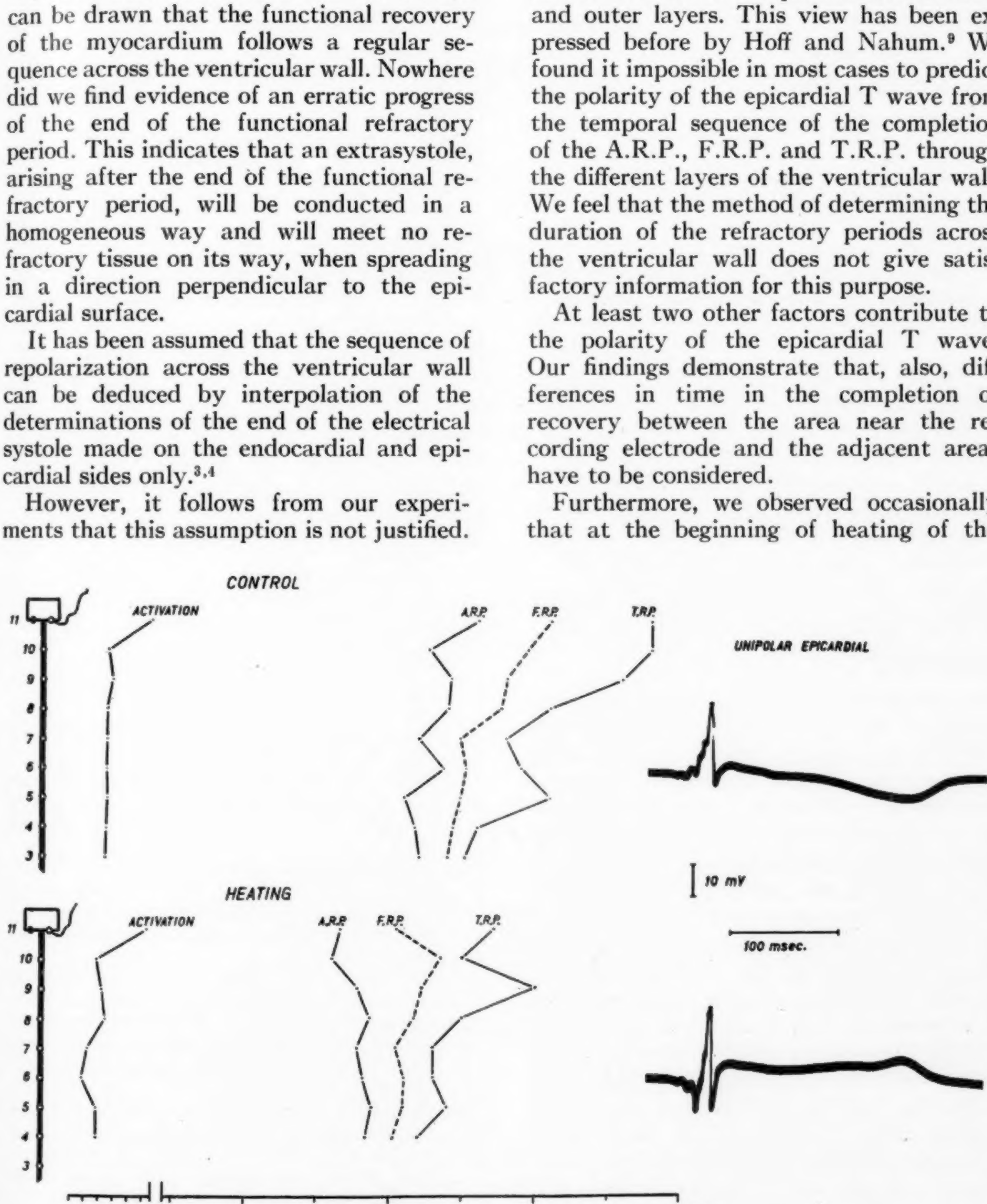

Fig. 5. Same explanation as for Fig. 4. *Upper part:* Control. *Lower part:* During heating of the epicardial surface. Experiment of Nov. 22, 1959. Needle electrode No. 1 as indicated in Fig. 6, inset. Discussion in text.

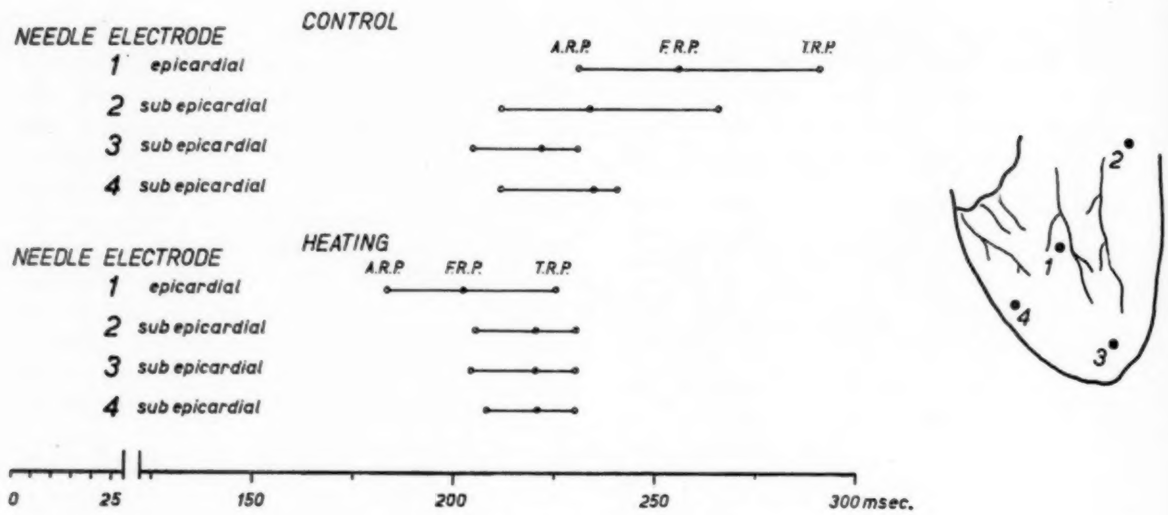

Fig. *6*. Same experiment as in Fig. 5. Temporal relations in recovery of excitability for unipolar cathodal stimulation of outermost terminals of 4 needle electrodes in the left ventricular wall of a dog's heart in situ. Duration of testing pulses is 0.5 msec. *Upper part:* Control. *Lower part:* During heating of epicardial surface around needle electrode. *Inset:* Position of needle electrodes. Discussion in text.

epicardial surface a positivity of the T wave could be replaced in a few seconds by a negativity by lifting the heating tube from the epicardial surface; positivity reappeared immediately when the heating tube was replaced on the epicardial surface. This means that in these cases the sequence of repolarization in the outermost layer was the only determining factor to the polarity of the epicardial T wave.

Summary

By means of needle electrodes the time course of excitability was studied at different depths of the left ventricular wall of intact dog hearts. The results indicate that the end of the functional refractory period progresses through the wall in an endocardial-epicardial direction and follows rather closely the pattern of activation. This progression does not follow a linear course indicated by the end of the refractory period at the endocardial and epicardial surfaces; in most cases recovery of excitability was more advanced in the middle layers than in the subendocardial and outer wall. Experiments in which the epicardial surface was heated or cooled indicate that the polarity of the T wave cannot be predicted from the general direction of recovery across the ventricular wall, but is also influenced by temporal differences in the completion of recovery between adjacent parts.

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Case reports

Bacterial endocarditis associated with atrial septal defect of the ostium secundum type

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Bacterial endocarditis is a rare complication of atrial septal defect of the ostium secundum type.[1-4] This observation is of particular interest since the defect is one of the most common congenital cardiac malformations seen at necropsy.[1,3] A review of the literature reveals only 4 cases of bacterial endocarditis associated with an isolated secundum atrial defect.[5-8]

The purpose of the present communication is to report an additional case of ostium secundum defect complicated by bacterial endocarditis. It was encountered in a study of 58 cases of bacterial endocarditis observed at the Babies Hospital in the past 30 years.[9]

Case report

Clinical data. The patient was a 23-month-old white female infant with a congenital cardiac malformation and urinary tract disease who was admitted to the hospital in 1939 because of fever.

PAST HISTORY. The infant was born at term and weighed 2.1 kilograms. A heart murmur was detected in the neonatal period. When the infant was 5 months of age, pyuria was noted in association with intermittent fever. There was marked retardation of growth and of pyschomotor development.

At 8 months of age, the infant was referred to the Babies Hospital for diagnostic evaluation. On examination at that time she was noted to be a small, poorly developed infant who perspired freely. She weighed 5.53 kilograms. There was no cyanosis or clubbing. A systolic thrill was palpable over the base of the precordium. Auscultation of the heart revealed a harsh systolic murmur which was maximal at the upper left sternal border; the pulmonic second sound was loud. The blood pressures obtained in an arm and a leg, while the infant was crying, were 104/70 and 118/? mm. Hg, respectively. An electrocardiogram indicated normal sinus rhythm, rate of 130, P-R interval of 0.16 second, and right axis deviation. A chest roentgenogram showed "cardiac enlargement." Congenital heart disease was diagnosed, although the nature of the defect was not defined.

Urinalyses revealed intermittent pyuria and mild albuminuria; specific gravity varied between 1.006 and 1.026. Specimens of urine for culture which were obtained by catheterization were frequently sterile but occasionally yielded growth of bacteria. The organisms which were recovered, either singly or in combination, included *Staphylococcus albus hemolyticus*, *Staphylococcus aureus hemolyticus*, and *Streptococcus hemolyticus*. An intravenous pyelogram demonstrated bilateral hydronephrosis and hydroureter; the right ureter was convoluted. Although obstruction was not visualized in the genitourinary tract, it was suspected at the ureterovesical junctions.

The patient remained in the hospital for 4 months and failed to show any gain in weight. Neurological evaluation suggested the diagnosis of congenital cerebral defect with spastic paraplegia and mental retardation. She had a few mild elevations of temperature for 1 to 2 days; the cause of the fever was usually obscure. The patient received no specific therapy and was discharged at 12 months of age.

PRESENT ILLNESS. Twelve days prior to readmission to the Babies Hospital, the infant became very irritable and was noted to have a fever of 103°F. Subsequent daily elevations of temperature occurred and reached a maximum of 106.5°F. She had anorexia and was lethargic.

PHYSICAL EXAMINATION. The vital signs recorded on admission were: temperature 102.4°F., pulse 140, and respirations 24. Systolic blood pressure,

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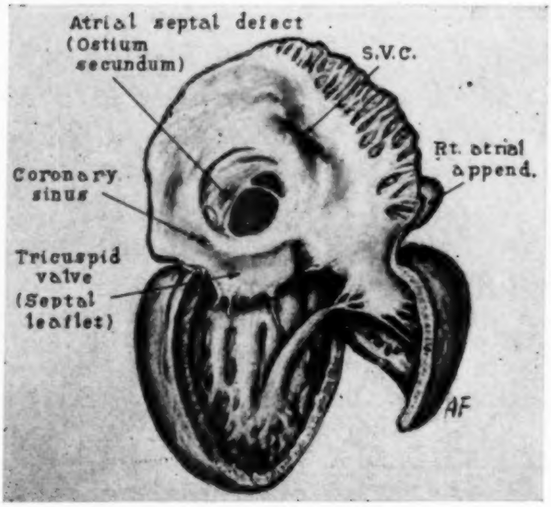

Fig. *1*. Drawing of the endocardial surface of the right atrium, tricuspid valve, and right ventricle. The atrial septal defect of the ostium secundum type lies within the valvula of the fossa ovalis.

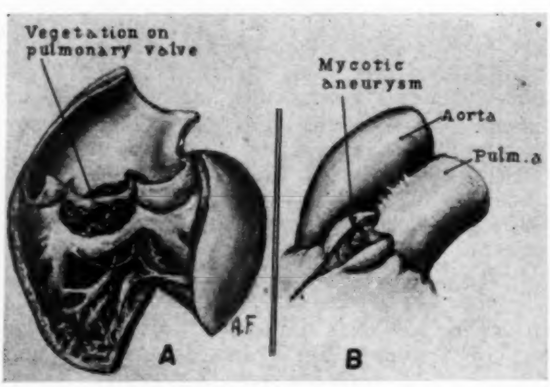

Fig. *2*. *A*, Drawing of the incised right ventricle, showing the bacterial vegetation on the right anterior cusp and sinus of the pulmonic valve. *B*, Drawing of the epicardial surface of the heart, showing a section through the mycotic aneurysm located at the right of the conus of the pulmonary artery.

determined by palpation, was 88 mm. Hg. She weighed 6.55 kilograms. The patient appeared to be marantic and poorly developed. The only positive physical finding was a harsh systolic murmur which was maximal at the left base. There was no evidence of petechiae, splenomegaly, or congestive heart failure.

LABORATORY DATA. The hemoglobin was 9.7 Gm./100 ml. The leukocyte count was 33,000/mm.^{3}, with 67 per cent polymorphonuclear cells. Analyses of blood revealed nonprotein nitrogen, 36 mg./100 ml.; carbon-dioxide combining power, 33.8 ml./100 ml.; serum calcium, 8.8 mg./100 ml.; and serum phosphorus, 4.1 mg./100 ml. Urinalysis showed 1+ albumin; in the sediment there were 15 to 45 white cells, 1 to 8 red cells, and a few hyaline and granular casts per high-power microscopic field. A urine culture revealed a few colonies of *Staphylococcus albus hemolyticus*. One blood culture was obtained which grew *Streptococcus hemolyticus:* this organism did not exhibit the typical characteristics of beta hemolysis and could not be classified as Group A. A chest roentgenogram on admission showed "cardiac enlargement especially at the base"; the lungs were clear.

COURSE IN THE HOSPITAL. The patient had a progressively downhill course, with daily elevations of temperature which ranged between 101° and 105°F. Sulfanilamide therapy (0.9 Gm. daily) was started on the third hospital day. On the fifth day she developed tachypnea and cyanosis, with signs of dullness over the left upper chest; these observations were supported by roentgenographic evidence of bilateral pulmonary infiltration which was interpreted as bronchopneumonia. The spleen became palpable on the sixth day. The patient expired on the seventh day.

Necropsy findings. The body was that of a poorly developed and undernourished female infant measuring 78 cm. in length and weighing 6.9 kilograms. The postmortem examination was limited to an abdominal incision. There were significant pathologic findings in the heart, lungs, and genitourinary tract.*

HEART. The heart was grossly enlarged and weighed 78 grams. There was a localized area of pericarditis over the outflow tract of the right ventricle. A hemispherical bulge, 0.5 cm. in height and 1.5 cm. in diameter, was present on the right side of the conus of the pulmonary artery: the surface of this protuberance was yellowish in color and studded with hemorrhages. The right atrium was dilated; its endocardium was smooth. In the anterior half of the valvula of the fossa ovalis there was a large atrial defect of the ostium secundum type; it measured 1.6 by 0.8 cm. and was divided by a narrow band (Fig. 1). The tricuspid valve was formed by three leaflets and appeared to be normal. The right ventricle was dilated and mildly hypertrophied; its wall was 0.5 cm. in thickness. There was no stenosis of the infundibulum or pulmonic ring. A huge reddish-brown fungating vegetation, which measured 2.5 by 1 by 1 cm., occupied the entire right anterior cusp and sinus of the pulmonic valve (Fig. 2,*A*). There were many tiny, light-brown plaques on the inferior surface of the left anterior cusp, ranging in size from pinpoint to 1 mm.; a few were also present on the posterior cusp. Section through the bulge on the epicardial surface of the right ventricle indicated a mycotic aneurysm, with friable vegetations occupying the entire cavity, communicating with the pulmonic valve (Fig. 2,*B*). The pulmonary veins drained normally into the left atrium; the endocardium was smooth. The mitral valve was formed by two leaflets and was normal in appearance. The endocardium of the left ventricle was smooth. The aortic valve was normal. The ductus arteriosus was closed. Measurements of the circumference of the valves, recorded before the heart was fixed, were as follows: tricuspid, 5.0 cm.; pulmonic, 3.4 cm.; mitral, 3.8 cm.; and aortic, 2.5 cm.

*The gross specimens and histologic sections of the organs described are in the Pathology Laboratory of the Babies Hospital (Case No. 6568).

Microscopic examination: (1) *Mycotic aneurysm*—The outer wall was composed of vascular connective tissue infiltrated with lymphocytes, polymorphonuclear leukocytes, and a few eosinophils. The central core was composed of vegetations consisting of granular eosinophilic material, bacteria, and leukocytes. The adjacent myocardium was edematous and showed loss of striations. The endocardium was replaced by a layer of degenerating muscle fibers with bacteria on the surface. (2) *Vegetation on the pulmonic valve*—This was composed of granular eosinophilic material in which were large clumps of bacteria and fragmented leukocytes. The surface of the vegetation appeared fibrinous. (3) *Plaques on the cusps of the pulmonic valve*—These consisted of bacteria superimposed on small areas of endothelial proliferation. Gram-positive cocci in pairs, short chains, and dense clumps were found in the sections through the mycotic aneurysm, the pulmonic vegetation, and plaques.

LUNGS. Gross infarcts were present in the upper and lower lobes of the right and left lungs. Friable thrombi were seen in the branches of the pulmonary artery leading to the areas of infarction. Clumps of Gram-positive bacteria were observed in some sections of the thrombotic material.

GENITOURINARY TRACT. The right kidney weighed 50 grams, and the left, 26 grams. The cut surface of the right kidney showed the architecture to be well preserved, whereas that of the left kidney was destroyed. The left renal pelvis and calyces were more markedly dilated than those on the right. Fine yellow gravel was present in the pelvis of each kidney. There were four large calculi in the right ureter. The ureters were tortuous, dilated, and had hypertrophied walls. Both ureterovesical junctions were patent but narrow. The bladder was dilated and hypertrophied; there was no obstruction or abnormality of the urethra.

Microscopic examination showed interstitial pyelonephritis of the left kidney. In the right kidney, numerous glomeruli contained capillary emboli. Chemical analysis of the ureteral calculi indicated calcium, phosphate, and large amounts of carbonate.

Anatomic diagnosis. (1) Bacterial endocarditis of the pulmonic valve with a mycotic aneurysm in the wall of the outflow tract of the right ventricle. (2) Congenital malformation of the heart: atrial septal defect of the ostium secundum type. (3) Infarcts of the right and left lungs. (4) Renal calculi, bilateral, and ureteral calculi, right. Hydronephrosis and hydroureter, bilateral. Interstitial pyelonephritis, left. Focal embolic glomerulonephritis, right. Hypertrophy and dilatation of the bladder (neurogenic?).

Discussion

The source of the bacteremia in this case was probably infection of the abnormal genitourinary tract. This is suggested by the history of intermittent pyuria since early infancy, the urographic evidence of bilateral hydronephrosis at 8 months of age, and the necropsy findings of renal and ureteral calculi formation and pyelonephritis. The organism which was recovered from blood culture, *Streptococcus hemolyticus*, may have been a member of the enterococcus group of streptococci. These organisms have frequently been incriminated in patients with genitourinary tract infection and endocarditis.[10]

The localization of the bacterial endocarditis on the pulmonic valve was most likely determined by the underlying congenital cardiac malformation, namely, atrial septal defect of the ostium secundum type. In cases of right-sided bacterial endocarditis without pre-existing heart disease the tricuspid valve is the most common site of infection.[3] The presence of a cardiac malformation predisposes specific endocardial sites to hemodynamic injury which favors the implantation of microorganisms during bacteremia. Traumatic endocardial lesions, resulting from the development of pressure gradients across a defect or a deformed valve, have been described in those cardiac anomalies commonly associated with bacterial endocarditis, e.g., ventricular septal defect, pulmonic stenosis, patent ductus arteriosus, etc. In large secundum atrial defect, however, left-to-right shunting of blood occurs through the defect without a significant pressure gradient. Endothelial "jet" lesions have not been described on the rim of the defect or in the atria, and patients with isolated secundum atrial defect are not prone to the development of bacterial endocarditis.[11]

There is evidence to suggest hemodynamic trauma to the pulmonic and tricuspid valves in ostium secundum atrial defect, which would theoretically increase the susceptibility to infection in these areas. The augmented blood flow from the intracardiac shunt may produce turbulence across the valves of the right heart. Intracardiac phonocardiography in patients with secundum atrial defect has provided indirect evidence of increased flow and vortex formation around these valves: murmurs which have been recorded in the right ventricle during diastole and in the pulmonary artery during systole are attributed to "functional" stenosis of the tricuspid and pulmonic valves, respectively.[12] Furthermore, observations from cardiac catheterization of patients with secundum atrial defect and large left-to-right shunts have

frequently documented pressure gradients across the pulmonic valve.[13] The disappearance of the gradient after surgical closure of the defect has verified the impression of relative pulmonic valvular stenosis due to increased flow. Since there have not been histologic observations of endocardial injury to the pulmonic and tricuspid valves in secundum atrial defect, one may infer that marked increase in pressure is a more important factor than flow in the production of hemodynamic lesions.

It is interesting to note in the necropsy findings of this case that there was endothelial proliferation underneath the small plaques of bacteria on two cusps of the pulmonic valve. These focal areas of fibrous reaction were probably a response to bacterial invasion, but they may also have been due to pre-existing hemodynamic trauma. The massive vegetation on the pulmonic valve was the source of multiple pulmonary emboli and infarcts. The mycotic aneurysm in the wall of the right ventricular outflow tract was probably caused by direct bacterial invasion from the pulmonic valve. The only evidence of systemic arterial embolization was mild focal embolic glomerulonephritis. The formation of peripheral emboli in cases of right-sided endocarditis in which there is no intracardiac right-to-left shunt may be related to pulmonary venous thrombosis, secondary to pulmonary infarction.[14]

The observations at postmortem examination in the present case are almost identical to those in the first case of bacterial endocarditis associated with an atrial septal defect described by Griffith[5] in 1906. He reported the necropsy of a 15-year-old girl with an ostium secundum defect which measured "one by one and a half inches," and endocarditis predominantly of the pulmonic valve. A huge fungating mass of vegetations which was attached to the valve communicated with a mycotic aneurysm at the base of the pulmonary artery and right ventricular outflow tract. It is of particular interest that the tricuspid valve was also involved; one small fibrinous vegetation was adherent to the commissure between the septal and anterior leaflets. The mitral valve was normal and free of inflammatory lesions.

In the other three cases of bacterial endocarditis with secundum atrial defect reported in the literature the localization of the vegetations was as follows: on the "limbus of the fossa ovalis and mitral valve" in one, on the left atrial wall in one, and not described in the third case, except for a statement that the rim of the defect was not involved.[6-8] In none of these reports was there a complete anatomic description of the heart; in only one of them were the size and position of the atrial defect and the appearance of the mitral valve noted.[7] These reports did not include either a bacteriologic diagnosis or a histologic description of the endocardial lesions. In the absence of this information the existence of bacterial endocarditis with an isolated ostium secundum defect in these cases is incompletely established.

The presence of deformities of the mitral or tricuspid valves may increase the susceptibility of patients with atrial septal defect to the development of bacterial endocarditis. Two cases of ostium secundum defect and mitral stenosis, the so-called Lutembacher syndrome, have been reported[15,16] in which bacterial vegetations occurred on the mitral valve. In ostium primum, or low atrial defect (partial form of common atrioventricular canal), malformations of the mitral and/or tricuspid leaflets invariably occur which may produce valvular insufficiency. Bacterial endocarditis in one case of ostium primum defect has been well documented[17]: the vegetations were implanted on the atrial surface of the cleft aortic leaflet of the mitral valve and extended onto the adjacent septal leaflet of the tricuspid valve. In her review of the incidence of bacterial endocarditis, Abbott[2] has tabulated 57 cases of atrial septal defect: among 44 with "defects of the upper portion (ostium secundum)," bacterial endocarditis was not present, whereas 6 of 13 with "defects of the lower portion" had this complication. The location of the vegetations in the cases with low atrial defect, presumably ostium primum, was not described.

Summary

The clinical and necropsy findings in a 23-month-old infant with an atrial septal defect of the ostium secundum type, com-

plicated by bacterial endocarditis, are presented. A massive vegetation was located on the pulmonic valve and communicated with a mycotic aneurysm in the wall of the right ventricular outflow tract. These lesions were almost identical to those described in the first reported case of endocarditis with ostium secundum defect. Three other cases recorded in the literature are reviewed.

Patients with large secundum atrial defect are not prone to the development of bacterial endocarditis, although there is evidence for hemodynamic turbulence and possible trauma to the valves of the right heart. It is suggested that additional deformities of the mitral and tricuspid valves may increase the susceptibility of patients with atrial septal defect to bacterial endocarditis.

The author wishes to express sincere appreciation to Dr. Dorothy H. Andersen for her interest and valuable help in reviewing the necropsy material of this case.

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Mechanisms influencing conduction in a case of intermittent bundle branch block

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The purpose of this report is to present a case of intermittent left bundle branch block in which the effects of a variety of physiologic maneuvers and pharmacologic agents were tested in an attempt to find trigger mechanisms which alter intraventricular conduction.

Previous authors, writing about the phenomenon of intermittent left bundle branch block, frequently raised the question of the mechanisms favoring normal and abnormal intraventricular conduction. Vessel[1] suggested that when a *critical heart rate* was exceeded, conduction through the diseased bundle became impaired and left bundle branch block was produced. In support of this theory, several authors[2-4] have presented case reports which showed that a small increase in heart rate was followed by a change from normal to aberrant intraventricular conduction. Other cases have been reported in which the alteration from normal to abnormal conduction was unattended by any change in heart rate. Finally, bundle branch block has been observed to develop during slowing of the heart rate.[5]

The present case afforded an opportunity for studying some of the variables involved in intermittent bundle branch block.

Case report

Present illness. This was the first admission to the Durham Veterans Administration Hospital for this 46-year-old white man. His chief complaint was chest pain on exertion. The patient had a documented anterior wall myocardial infarction which had occurred 14 months prior to admission. He gave no history of previous angina pectoris. Subsequent to the myocardial infarction the patient had been unable to work because of recurrent oppressive substernal chest pain on exertion or with excitement. He also gave a history of mild shortness of breath on exertion, but denied orthopnea, nocturnal dyspnea, or edema. Four years prior to admission the patient was found to have mild hypertension. One year prior to admission the patient was told that his electrocardiogram showed some form of heart block.

Physical examination. The blood pressure was 130/80 mm. Hg, pulse 92, and respirations 12. The patient was a well-developed, slightly obese white man. Examination of the eye grounds showed Grade I hypertensive retinopathy. Examination of the chest revealed a few moist râles at the base of the left lung. The heart was enlarged to the left. The heart sounds were normal, with a prominent atrial gallop and a faint ventricular gallop. Upon examination of the abdomen, the edge of the liver was palpable two fingerbreadths below the right costal border. The remainder of the physical examination was within normal limits.

Accessory clinical findings. Hemoglobin was 16.2 Gm. per cent, with normal white blood cell count and differential. Urinalysis was normal. Stool guaiac was negative. The chest x-ray examination showed cardiomegaly, with a cardiothoracic ratio of 15.2/28.2. Chemistries were reported as follows: fasting

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blood sugar, 106, blood urea nitrogen, 20, cholesterol, 239, total protein, 6.9 with a normal A/G ratio. Gall-bladder series was reported to be normal. Phenolsulfonphthalein test was 75 per cent in 2 hours. The initial electrocardiogram was interpreted as showing left bundle branch block. A second electrocardiogram recorded 2 days later showed normal intraventricular conduction, with a prominent Q wave in Lead aV_L and absent R waves in the right precordial leads.

Methods

The physiologic maneuvers studied were performed under constant electrocardiographic monitoring. Control tracings were made with the patient lying quietly on an examining table. Exercise was studied by having the patient leg pedal with maximum effort while in the supine position, or, on occasion, do rapid deep knee bends in the standing position. Valsalva and Müller maneuvers were performed in the usual way and were held for a period of 20 to 30 seconds. When arterial occlusive cuffs were used, they were placed around all four extremities and released after a 5-minute period. Alterations in blood gas were induced by having the subject inhale 10 per cent oxygen or 10 per cent carbon dioxide for 3 to 5 minutes. Carotid sinus pressure was applied to the right side for varying periods of time and with varying force. Ocular pressure was applied over both eyeballs simultaneously. Between studies there was a period of rest and equilibration.

Pharmacologic agents were administered to the subject under electrocardiographic monitoring. The drugs, dosages, modes of administration, and results of each are listed in Table II. All of the agents were administered intravenously except for Mecholyl and amyl nitrite, which were given subcutaneously and by inhalation, respectively.

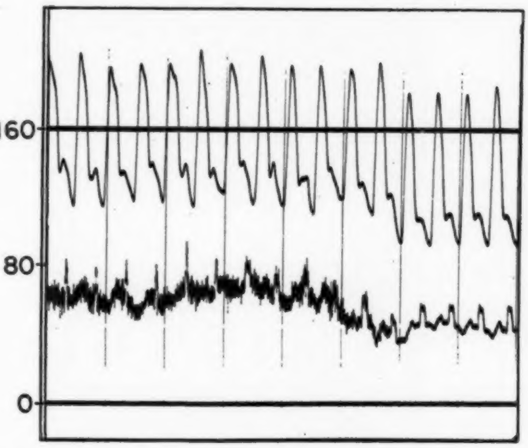

Fig. 1. Exercise.

Blood pressures were determined with the standard cuff and, on occasion, were measured directly from an intra-arterial needle, with the use of a Statham strain gauge and a photographic recorder.

Results

Results of the various physiologic maneuvers are summarized in Table I. Exercise served as a consistent method of producing aberrant conduction (Fig. 1). At least 15 seconds of exercise by the patient in the supine position were required before conversion of normal conduction to bundle branch block. During this time there was an increase in heart rate of 40 to 60 beats per minute, and a rise of blood pressure from control levels of 140/90 to 200/120 mm. Hg. With the patient in the upright

Table I. *Physiologic maneuvers performed*

Maneuver	*Control period*		*Response*	
	Rate	*Conduction*	*Rate*	*Conduction*
Exercise supine	80–115	Normal	120–140	Left bundle branch block
Exercise standing	90–115	Normal	117–140	Left bundle branch block
Arterial cuff release	90–120	Normal	125–130	Left bundle branch block
Valsalva maneuver	100–110	Normal	120–130	Normal
Müller maneuver	90–110	Normal	70–100	Normal
Oxygen—10 per cent	100	Normal	140	Normal
Carbon dioxide—10 per cent	108	Normal	135	Normal
Carotid sinus pressure	94–122	Left bundle branch block	72–98	Normal
Carotid sinus pressure	80–100	Normal	45–60	Left bundle branch block
Ocular pressure	100–120	Left bundle branch block	105	Left bundle branch block

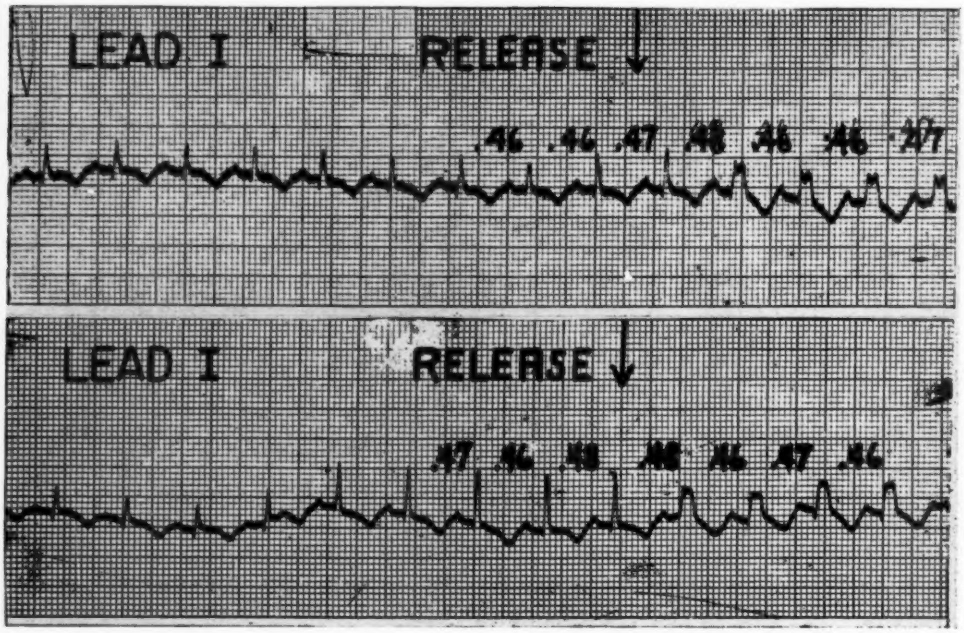

Fig. *2*. Valsalva maneuver.

position, aberrant conduction followed one to ten deep knee bends. When conversion occurred after only one knee bend, the heart rate had increased by only two beats per minute. On other occasions, as many as ten knee bends were performed prior to conversion, and there was an associated increase in heart rate of 20 to 50 beats per minute.

The release of arterial occlusive cuffs when the patient was in the standing position resulted in conversion to bundle branch block within 10 seconds; this was associated with an increase in heart rate of 10 to 25 beats per minute.

The Valsalva maneuver produced an increase in heart rate of 10 to 30 beats per minute, with maintenance of normal intraventricular conduction. Upon *release* of the Valsalva maneuver, normal conduction converted to bundle branch block within one to three beats on several occasions (Fig. 2). Aberrant conduction did not occur on release of the Valsalva maneuver while arterial pressures were being recorded. However, it can be seen from Fig. 3 that mean and diastolic blood pressures reached very low levels during the period immediately after release of the Valsalva maneuver. The Müller maneuver had only a slight effect on heart rate and did not alter intraventricular conduction.

Inhalation of 10 per cent oxygen or 10 per cent carbon dioxide led to a tachycardia of 130 to 140 beats per minute, without any change in intraventricular conduction. It was also noted that the breathing of 100 per cent oxygen did not prevent the consistent conversion to bundle branch block after exercise.

The various responses to carotid sinus pressure are illustrated in Fig. 4. The arrows indicate the points at which carotid sinus pressure was applied. Tracing *A* demonstrates the ease with which bundle branch block could be converted to normal intraventricular conduction with light carotid sinus pressure. Tracings *B*, *C*, and *E* illustrate the responses to more forceful carotid sinus pressure. In each case it can

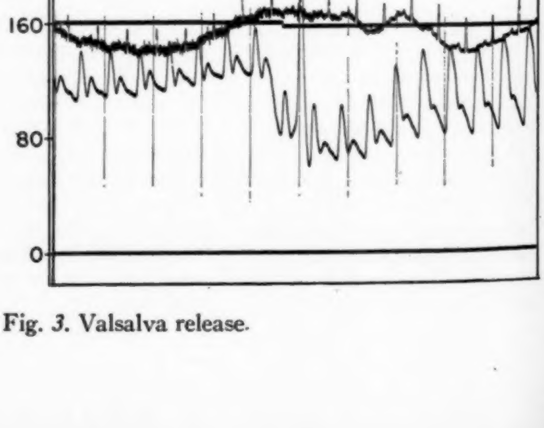

Fig. *3*. Valsalva release.

be seen that aberrant conduction followed a period of prolonged asystole and was then followed by conversion to normal intraventricular conduction. Tracing *F* illustrates that atropine blocked the effects of carotid sinus pressure on bundle branch block induced by exercise. Tracing *G* shows that bundle branch block beats persisted during prolonged carotid sinus pressure in spite of marked bradycardia. The finding of aberrant beats during vagal-induced bradycardia led us to examine the effects of carotid sinus pressure on normal conduction. Tracing *D* illustrates such a study and demonstrates that carotid sinus pressure can induce bundle branch block. In Fig. 5 it is shown that the conversion to bundle branch block during carotid sinus pressure is associated with a prolonged period of asystole and is attended by a marked fall in mean arterial blood pressure.

The results of the studies in which pharmacologic agents were given are presented in Table II. Potassium and Pronestyl each resulted in conversion of normal conduction to bundle branch block. On separate occasions, conversion occurred during an increase, decrease, or no change in heart rate. Calcium or molar sodium lactate rapidly converted bundle branch block induced by potassium or Pronestyl to normal intraventricular conduction.

Inhalation of amyl nitrite when the patient was in the standing position resulted in a change from normal to aberrant conduction, with an associated increase in heart rate of only two beats per minute. Inhalation when he was in the supine position had no effect on intraventricular conduction.

Atropine produced a tachycardia of 122 beats per minute, without any change in intraventricular conduction.

The administration of Isuprel resulted in an increase in heart rate from a control level of 88 beats per minute to 170 beats per minute. There was no change from normal intraventricular conduction throughout the period of infusion. Transiently during this study the P-R interval shortened from a control of 0.20 to 0.08 second. We have observed similar shortening of the P-R interval in normal subjects during infusion of Isuprel, over and above the shortening associated with increased heart rate.

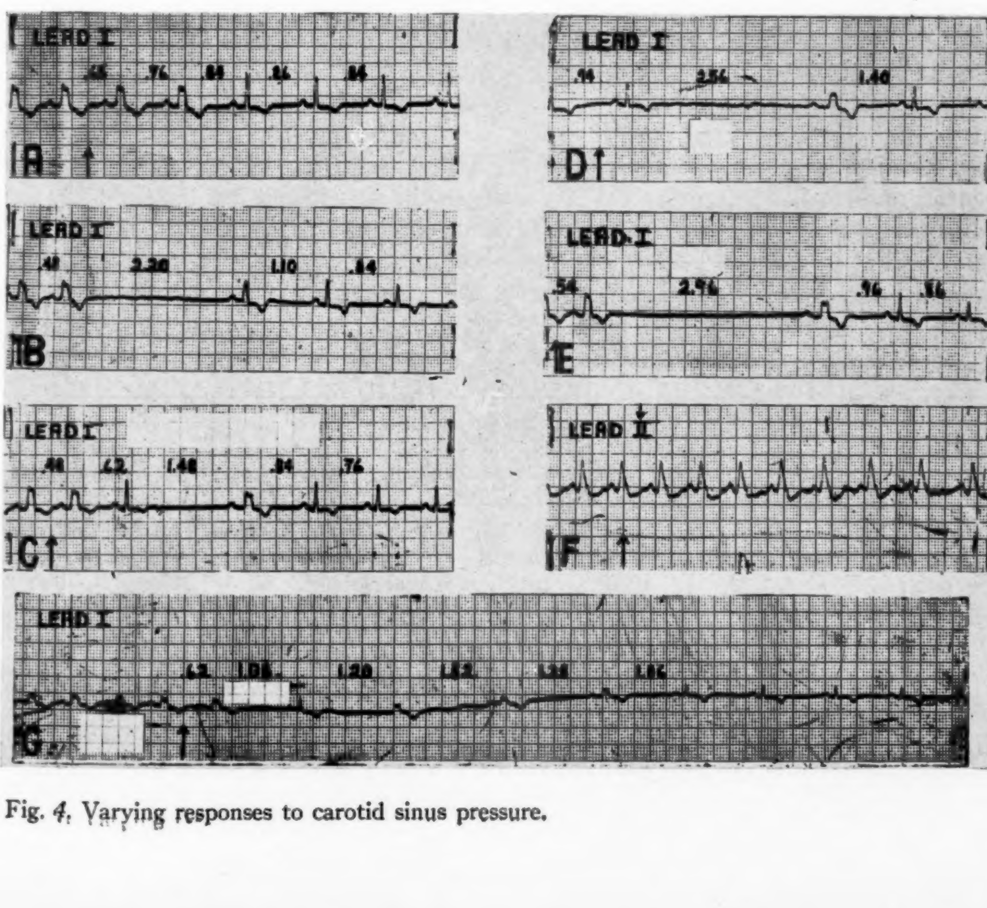

Fig. 4. Varying responses to carotid sinus pressure.

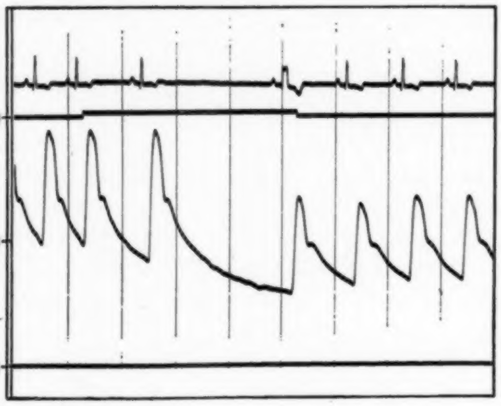

Fig. 5. Carotid sinus pressure.

Tensilon, Mecholyl, and aminophylline had only slight effects on cardiac rate and did not lead to any alteration in intraventricular conduction.

Discussion

The case reported illustrates the phenomenon of intermittent left bundle branch block. Unstable bundle branch block of this type was first described by Lewis[6] in 1913. This is not a rare conduction abnormality, as Comeau, Hamilton and White[7] noted in 1938. They also pointed out that most cases of intermittent left bundle branch block occurred in a setting of organic heart disease. The etiology of the conduction disturbance in this case was presumed to be coronary artery disease, based on a history of angina pectoris and a documented myocardial infarction.

Mechanisms favoring normal and abnormal conduction in cases of intermittent left bundle branch block have been discussed by many clinical investigators over a 30-year period. Vessel[8] reported two cases which clearly demonstrated that this type of intraventricular conduction may be very susceptible to changes in cardiac rate. Eichert[9] showed that whereas rapid heart rates favored conversion to bundle branch block, and slow heart rates favored normal conduction, there was considerable overlap between the two forms of conduction with respect to rate.

Exercise served as a consistent way of inducing left bundle branch block in our patient. It was our initial impression that conversion to left bundle branch block with exercise was related to the associated increase in heart rate. We attempted to evaluate this hypothesis by inducing tachycardia comparable to that produced by exercise, using atropine, Isuprel, or inhalation of carbon dioxide. Tachycardia induced by these agents failed to produce bundle branch block.

Termination of bundle branch block by carotid sinus pressure has been reported previously and has been attributed to slowing of the heart rate below a critical level.[10,11] In our patient, carotid sinus pressure served as a consistent method of converting bundle branch block to normal intraventricular conduction. However, we noted that during *forceful* carotid sinus pressure, blocked conduction persisted for several beats despite marked bradycardia. To our surprise we also noted that forceful carotid sinus pressure consistently induced conversion from normal intraventricular conduction to bundle branch block. This case appears to be unique by being the first

Table II. Pharmacologic agents administered

Agent	Dose	Control period		Response	
		Rate	Conduction	Rate	Conduction
Pronestyl	200 mg. I. V.	110-118	Normal	95-100	Left bundle branch block
Potassium	40 mEq. I. V.	94-100	Normal	92-108	Left bundle branch block
Calcium gluconate	1.0 Gm. I. V.	100	Left bundle branch block	85	Normal
Molar sodium lactate	100 mEq. I. V.	102	Left bundle branch block	84	Normal
Amyl nitrite	Inhalation	120	Normal	122	Left bundle branch block
Atropine	2.0 mg. I. V.	100	Normal	122	Normal
Isuprel	.004 mg./min. I. V.	88	Normal	170	Normal
Aminophylline	500 mg. I. V.	102	Normal	118	Normal
Mecholyl	20 mg. subcutaneously	110	Normal	116	Normal
Tensilon	1.0 mg. I. V.	100	Left bundle branch block	84	Left bundle branch block

in which carotid sinus pressure both terminated and induced bundle branch block in the same patient.

The observations made on the patient during exercise, pharmacologically induced tachycardia, and carotid sinus pressure illustrate that both bundle branch block and normal intraventricular conduction may occur at slow and rapid heart rates. Normal conduction was recorded at heart rates from 58 to 172; bundle branch block was recorded at heart rates from 45 to 160. It is our opinion that this wide overlap (Fig. 6) eliminates heart rate per se as the primary determinant of the type of intraventricular conduction in this patient.

It was our impression that the type of intraventricular conduction during carotid sinus pressure was related to the force applied to the sinus. In an attempt to evaluate this hypothesis we sought to establish what relationship, if any, existed between the degree of prolongation of the R-R interval and the form of the ventricular complex. This relationship is illustrated in Fig. 7. When, during carotid sinus pressure, the R-R interval was less than 1.2 seconds, the

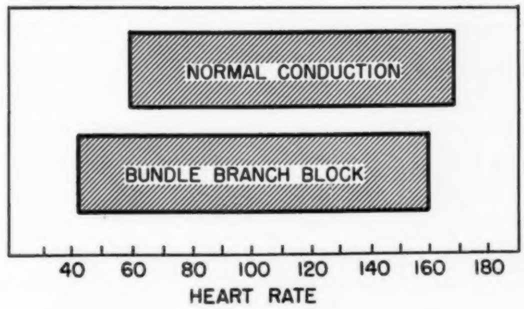

Fig. 6. Heart rates with normal conduction and bundle branch block.

ventricular complex was normal. When the R-R interval was greater than 1.4 seconds, the form of the ventricular complex was that of left bundle branch block. This relationship held regardless of the type of intraventricular conduction prior to carotid sinus stimulation. It is tempting to postulate from this data that increased vagal tone can itself induce bundle branch block, but it will be seen from subsequent discussion that alternative mechanisms may be operative, and that a cause-and-effect relationship has not been demonstrated.

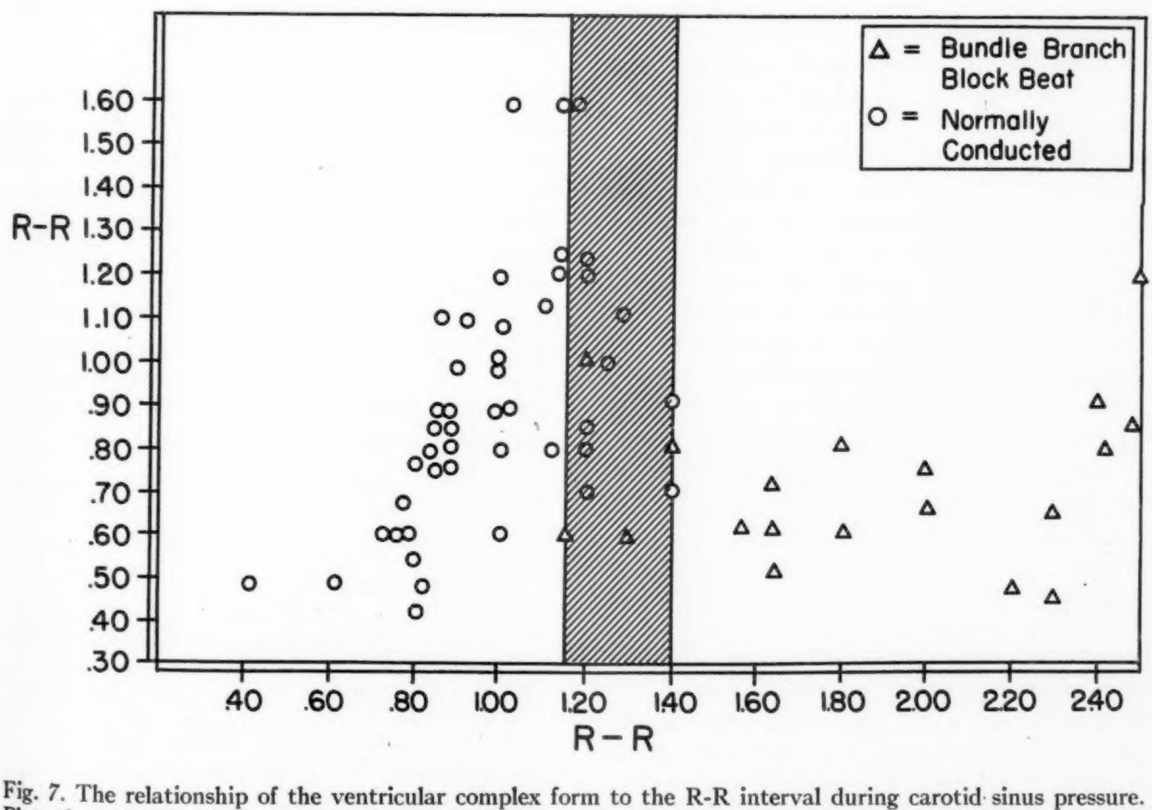

Fig. 7. The relationship of the ventricular complex form to the R-R interval during carotid sinus pressure. Plotted on the abscissa are the R-R intervals between each beat recorded during carotid sinus pressure. For purpose of spread only, the R-R intervals preceding that recorded on the abscissa are plotted on the ordinate.

Inhalation of amyl nitrite and release of arterial occlusive cuffs when the patient was in the standing position led to aberrant conduction with little change in heart rate. On release of the Valsalva maneuver, conversion to bundle branch block occurred within one to three beats on several occasions. A hemodynamic sequel common to these three maneuvers is a fall in arterial blood pressure, and it may be that this led to reduced coronary perfusion and bundle branch block in these instances. In this regard it is also interesting to recall that during carotid sinus pressure there was a significant fall in arterial pressure during the period of asystole preceding conversion to bundle branch block. Dressler[5] recently reported two cases in which normal intraventricular conduction converted to left bundle branch block under circumstances of increased vagal tone. He proposed the theory that increased vagal tone may induce bundle branch block by a (postulated) coronary vasoconstrictor effect. Coronary blood flow was not measured in our patient, and, therefore, no conclusions regarding its effect can be drawn. Reduced coronary blood flow is still a plausible explanation for the induction of bundle branch block.

Of the pharmacologic agents given, those known to depress intraventricular conduction, i.e., Pronestyl and potassium, induced bundle branch block. Agents known to facilitate intraventricular conduction, i.e., calcium and molar sodium lactate, reversed the effects of Pronestyl and potassium and converted bundle branch block to normal conduction. These responses suggest that the diseased bundle may be sensitive to influences which primarily alter conductivity.

In conclusion, it was our purpose to elucidate trigger mechanisms which served to alter intraventricular conduction in a patient who demonstrated the phenomenon of unstable bundle branch block. It is apparent that these trigger mechanisms are sufficiently complex to defy any simple explanation. Maneuvers of the type performed on this patient do offer possible avenues for further investigation. Such studies may ultimately clarify the interrelationships between hemodynamic, neural, and nutritional factors and the fundamental process of impulse transmission in the normal and diseased heart.

Summary

A case study of the phenomenon of intermittent left bundle branch block has been presented. We tested a variety of physiologic maneuvers and pharmacologic agents for their effects on intraventricular conduction. The data indicated that heart rate could not have been the primary determinant of the type of intraventricular conduction, but may have had a secondary or modifying influence. Carotid sinus pressure was shown to both terminate and induce bundle branch block. The form of the ventricular complex during carotid sinus pressure was related to the degree of prolongation of the R-R interval. It could not be determined from our data whether the response to increased vagal tone was due to direct inhibitory effect of the vagus or to other factors, such as the marked fall in mean arterial blood pressure. The effects of the various physiologic maneuvers suggest that hemodynamic factors may play a major role in determining the form of the ventricular complex. The responses to the various pharmacologic agents tested seemed to indicate that the diseased bundle was extremely sensitive to influences primarily altering intraventricular conductivity.

In conclusion, after a careful analysis of studies performed on a patient with intermittent left bundle branch block, we still do not know which factor(s) was (were) most important in governing the mode of intraventricular conduction. It appears that heart rate can be eliminated as a primary factor in this patient. Perhaps the final answer to this problem lies in a better understanding of the interaction of hemodynamic, neural, and nutritional factors on intraventricular conduction.

We wish to thank Dr. Eugene A. Stead, Jr., Dr. E. Harvey Estes, Jr., and Dr. Henry D. McIntosh for their assistance with this report.

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Review

Alcoholic cardiomyopathy

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It is now custom to apply the term *cardiomyopathy* to any affection, including hypertrophy, of the myocardium, which is not part of such common states as hypertension, or coronary arterial, valvular, and congenital heart disease. Only within recent times has it become known that alcohol is a frequent cause.

The delay in such recognition is explained by a set of circumstances which include the stealthy development of the condition, the sparsity of physical signs in its early stages, a misinterpretation of the cause of an arrhythmia which it commonly exhibits, the erroneous assumption that the harmful effects of alcoholism make themselves known as a beriberi syndrome, the wrongful conclusion that certain electrocardiographic changes and, later on, heart enlargement with heart failure have been the outcome of coronary arterial disease, and the inattention paid to insular changes in a hypertrophied myocardium at necropsy.

Because alcoholic cardiomyopathy in its early stages can be halted, its prompt diagnosis is rewarding, for abstinence from spirit-drinking before it has exerted serious and irretrievable damage on the heart muscle will enable a patient to regain his customary health. A familiarity with its clinical and electrocardiographic presentation, therefore, assumes exceptional importance.

Clinical features

The chief characteristic which marks the progress of the injurious effects of alcohol on the heart is the insidious way in which they creep in. Thus, many months or even years may pass before the undisguised spectacle of cardiac involvement is laid bare.

Palpitation may be the first symptom to appear in alcoholic cardiomyopathy, taking the form either of paroxysmal tachycardia or more often of auricular fibrillation. Indeed, fibrillation in the absence of its more common causes, such as mitral stenosis, thyroid toxemia, cardiac infarction, hypertension, and constrictive pericarditis, is likely to be the outcome of excessive spirit-drinking, and in this circumstance it is for the clinician to extract this confession through persistent interrogation of the patient, or his relatives if necessary.

Of great significance too is the finding in an adult of extrasystoles in company with a moderate tachycardia of 90 or so per minute. It should be recalled that extrasystoles do not like tachycardia, so that if these two states are found side by side, cardiomyopathy from alcoholism is the usual explanation.

Bundle branch block, either in sinus rhythm or associated with fibrillation, is a common conduction defect, and complete heart block is not rare.

Moderate *breathlessness* is also a common initial symptom. In that the complaint is not an arresting one during the early phase of the illness, it is not infrequently attributed to obesity, which is almost invariably present.

Chest pain is not a symptom of alcoholic

From the Cardiac Department, London Hospital, London, England.
Received for publication July 18, 1960.

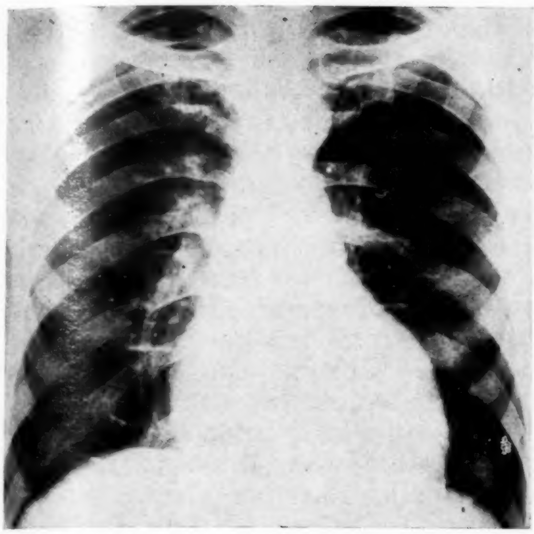

Fig. *1*. Moderate enlargement of the heart, with early pulmonary congestion.

cardiomyopathy, but should it be a fortuitous finding, it gains importance when the subsequent electrocardiogram shows changes which may lead erroneously to the assumption that cardiac infarction is providing a source for the pain.

At a *later stage* of the illness, breathlessness increases and becomes a distressing symptom, for it is then accompanied by the more sinister signs of heart failure, which include a prominent venous pulse which frequently shows a diastolic dip, greater cardiac enlargement, triple heart rhythm, a pansystolic murmur from dilatation of the mitral or tricuspid rings initiating mitral or tricuspid regurgitation, crepitations at the lung bases over which fluid collects, and even edema of the ankles.

Radiology. During the early phase of the illness, the heart, when viewed radiologically, may appear natural in shape and in size. When the T wave in the electrocardiogram becomes deformed, even in a limited way, some degree of cardiac enlargement is common. As the condition progresses, such enlargement assumes prominence, and hilar clouding makes its appearance as evidence that heart failure has set in (Figs. 1 and 2). Sometimes, the cardiac silhouette is large because of the addition of pericardial effusion. If a beriberi syndrome has developed, much pulmonary congestion may show in the absence of conspicuous cardiac enlargement.

The beriberi syndrome. In those patients who consume large quantities of alcohol, especially in the form of beer, to the exclusion of regular and adequate meals, the body is supplied with a surfeit of calories from a high intake of carbohydrates but is deficient in vitamin B_1. Thus, a clinical syndrome results in the occident similar to that styled as beriberi in the orient, one which develops when polished rice forms the staple article of diet.

The clinical features arising from such thiamine deficiency include the accumulation of fluid in serous cavities, anasarca, warm skin, a pounding arterial pulse with a raised pulse pressure, and increased circulation time, characterizing the so-called *high output* heart failure. At the height of the illness the electrocardiogram may be surprisingly normal, but as soon as satisfactory diuresis and clinical improvement take place after treatment with thiamine, the tracing usually shows sharp and temporary inversion of T waves. Presumably, such characteristic fugitive changes result from an abrupt mobilization of electrolytes within the myocardium after the beneficial action of thiamine.

The purpose of this paper, however, is to emphasize the rarity of this beriberi syndrome among those who drink spirits in excess, at least in my own country, and to name this circumstance as among the chief reasons for our erstwhile neglect to

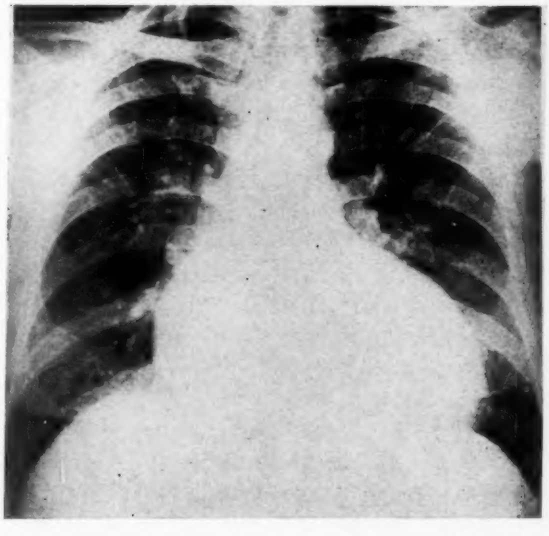

Fig. *2*. Great enlargement of the heart, hiding the hilar congestion.

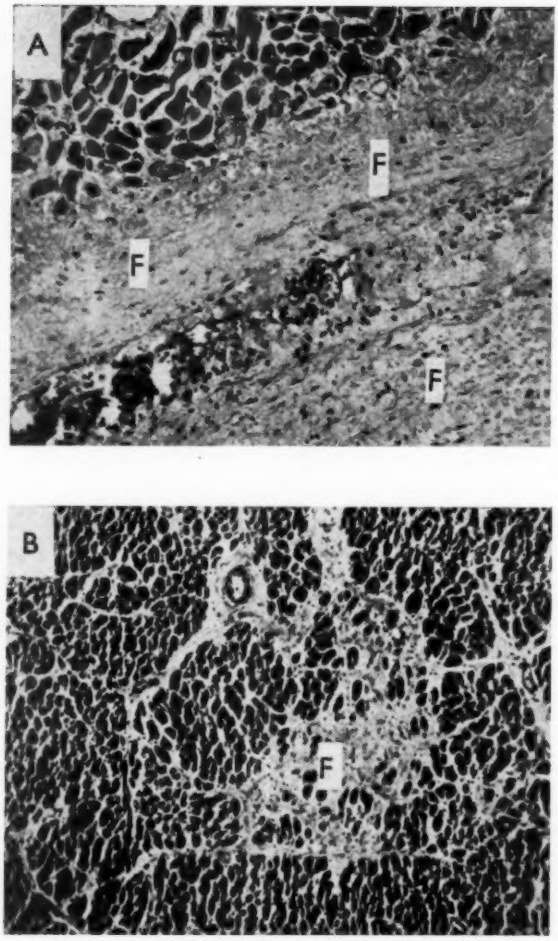

Fig. *3*. Dense fibrosis (*F*) of the myocardium in *A*, and sparse fibrosis (*F*) in *B*.

recognize the deleterious effects of alcohol on the heart muscle. In turn, it is meant to call into prominence those clinical and electrocardiographic features which enable a readier diagnosis of alcoholic cardiomyopathy, a common and preventable form of heart disease.

Nature of the myocardial injury. Before discussing the separate electrocardiographic patterns which characterize alcoholic cardiomyopathy, it is expedient to describe the myocardial lesion, because the former are better understood when they are related to the corresponding histologic changes in the heart muscle.

Thus far, the pathologic changes wrought by alcohol on the myocardium have not been universally appreciated, and this neglect partly follows a habit of years to regard alcohol as showing a proneness to assault the liver rather than the heart. It is the heart, however, which is the first exponent of the injurious effects of alcohol in man. The recognition of the cardiac injury at this stage carries a hope that the damage which the condition inflicts can be retarded and to some extent reversed. To allow it to go unheeded until it has spread to involve large areas of the heart, causing the heart to enlarge and to fail, is to forfeit this opportunity to do good; to ignore cardiac fibrosis during the wait for hepatic fibrosis to develop, is to wait too long, for it is not then within the competence of therapeutic management to bring about any material improvement. The pathologic changes which take place, and in the absence of coronary arterial disease, are in two groups, being either sparse or gross.

In the *sparse* variety (Fig. 3) the heart may show some enlargement from compensatory hypertrophy of its muscular fibers. Macroscopically, the cut surface of the myocardium may appear to be normal. Likewise, a cursory histologic examination may fail to discover anything wrong, but a more diligent search will find insular areas of fibrosis, accompanied by a variable degree of cellular reaction. Not infrequently, such a lesion may lie astride the path of the conducting tissue.

The more *gross* changes (Fig. 3), consisting of larger and more confluent areas of fibrosis, are discernible to the naked eye, and cardiac enlargement, from compensatory hypertrophy of the muscle fibers, is a more obvious feature.

The electrocardiogram

The electrocardiogram has proved itself of inestimable value in the diagnosis of alcoholic cardiomyopathy, and characteristic blemishes in the tracing established that heavy spirit-drinking accounted for the symptomatology in 80 patients assembled in private practice over a relatively short period, most of whom attempted to

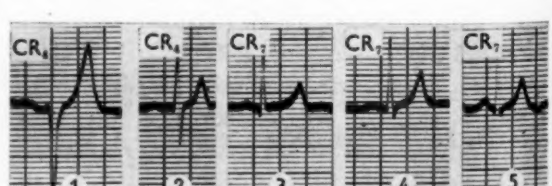

Fig. *4*. Spinous T waves from five patients.

conceal this habit until persistent questioning eventually brought forth an admission.

The abnormality in the electrocardiogram takes the form of either a deformity in the T wave, some kind of arrhythmia, or a fault in conduction, and the changes are conveniently described under these three heads.

Distinctive T-wave changes. For the most part, T-wave changes result from myocardial lesions which have already been described as *sparse* pathologic changes, so that a limited aggregate of fibers are interrupted and contrasting with the considerable portions of heart muscle involved when the blood supply is deprived by occlusive disease of the coronary arteries.

THE SPINOUS T WAVE. In this deformity the summit of the T is drawn out to a needle-like point (Fig. 4). As a rule, the T is at the same time tall. It is seen in leads over the left ventricle, but since tall and rather spiky T waves are seen in the apical Lead CR_4 in healthy subjects, this near-normal T wave is more readily discerned in the posterior axillary Lead CR_7. For this reason, should V leads be recorded instead of CR leads, this distinctive electrocardiographic sign may not show to the same advantage.

The spinous T wave indicates an increased rather than impeded conductivity across the muscle because of a state of increased irritability, and so constitutes the earliest evidence of the toxic effect of alcohol on the myocardium.

THE CLOVEN T WAVE. This deformity appears as a cleft at the summit of a T wave

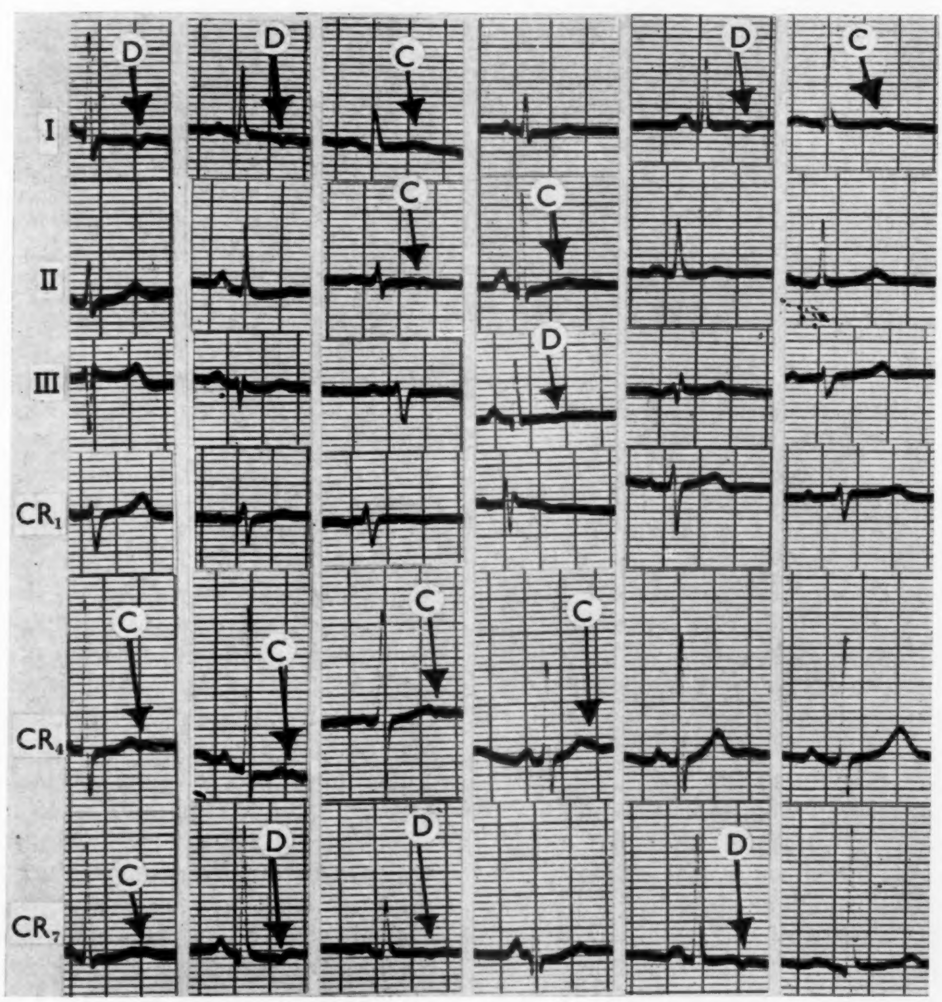

Fig. 5. The electrocardiogram in six patients, showing cloven (*C*), dimple (*D*), and low T waves.

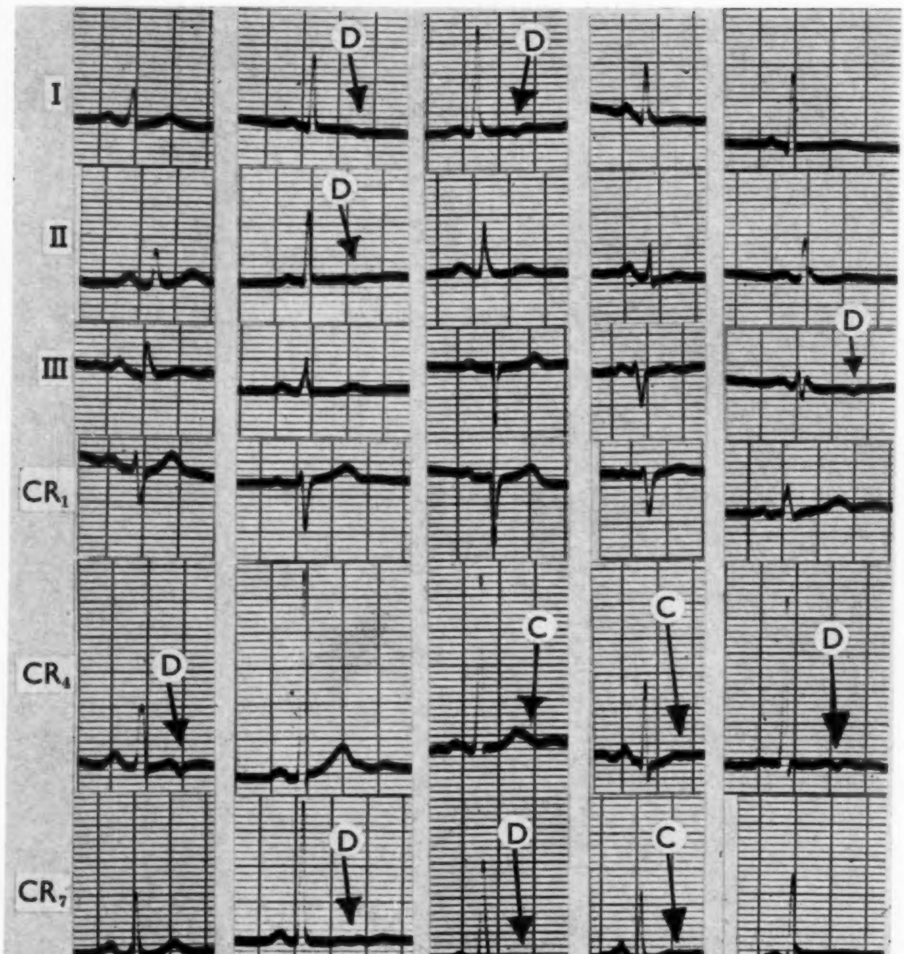

Fig. *6*. The electrocardiogram in five patients, showing cloven (*C*), dimple (*D*), and low T waves.

which is somewhat subdued in height, and is usually seen in Leads I, II, or CR_4 (*C* in Figs. 5 and 6). It is known that a cloven T wave may appear in the apical lead in healthy children, but in this event the T is deformed to a greater extent in the right ventricular leads. Rarely, the cloven T may be the outcome of a very limited cardiac infarction, but in practice it may be assumed that this deformity of the T in left ventricular leads in a patient without chest pain signals the diagnosis of alcoholic cardiomyopathy, and its presence should direct inquiry into the amount of spirits habitually consumed. A cloven T can remain apparent in the presence of fibrillation, provided that the effects of neither digitalis nor transient bundle branch block have been added. Abstinence from spirit-drinking may cause this distinctive electrocardiographic sign to disappear, in concert with loss of all symptoms (Fig. 7).

THE DIMPLE T WAVE. Herein lies another characteristic electrocardiographic deformity in early alcoholic affection of the myocardium. The S-U period is isoelectric, except for an interruption by a shallow and narrow dimple (*D* in Figs. 5 and 6). This dimple T is commonly found in Leads I and CR_7, and sometimes in Lead CR_4.

Occasionally, a dimple T has appeared in young subjects after a meal, but this postprandial electrocardiographic change disappears in the course of a few hours. Should the sign be met with rarely in a patient with cardiac pain, it is never a lone abnormality and it occurs alongside more obvious changes in other leads, including

significant Q waves, deep and wide T-wave inversion, and depression of the S-T segment.

When either cloven or dimple T waves are exhibited, T waves in other leads are often of low voltage.

FRANK T-WAVE INVERSION. With the passage of time and the spread afield of myocardial fibrosis, the newly described distinctive deformity of the T wave in certain leads may be accompanied by deeper inversion of the T wave in other leads, but even in this circumstance the base of the T wave is not so wide as in those patients in whom the electrocardiogram signifies cardiac infarction from coronary arterial disease (Fig. 8).

Arrhythmia.

EXTRASYSTOLES. When the clinical features of alcoholic cardiomyopathy were described earlier, emphasis was given to the presence of extrasystoles in the company of tachycardia. The electrocardiogram in this instance, in addition to confirming the rather unusual combination, shows that the frequent premature beats commonly take origin from multiple foci in the heart (Fig. 9).

PAROXYSMAL TACHYCARDIA. Because this innocent rhythm is so often exhibited in healthy subjects, care should be taken before attributing it to heavy spirit-drinking. Nonetheless, when auricular tachycardia appears for the first time in an adult male, alcoholic cardiomyopathy should be kept in mind as a possible cause, and the distinctive electrocardiographic signs should be sought whenever sinus rhythm is resumed.

AURICULAR FIBRILLATION. When the common causes of fibrillation, like mitral stenosis, thyroid toxemia, cardiac infarction, hypertension, and constrictive pericarditis, have been excluded in a given patient, it should be known that it may often assume one of two other forms, namely, the lone kind of fibrillation, or one which has its source in alcoholic cardiomyopathy. The latter can be told from the former by the quicker heart rate, the association of some degree of cardiac enlargement, and the presence of one of the distinctive T-wave changes, or multifocal extrasystoles, in the electrocardiogram (Fig. 10).

To bear in mind excessive spirit-drinking as the cause of paroxysmal, or established, auricular fibrillation in the adult, and to examine the electrocardiogram critically before digitalization has deformed it, is to re-emphasize the common incidence of alcoholic cardiomyopathy.

Faulty conduction. Mention has already been made, when description of the sparse pathologic changes in alcoholic cardiomyopathy was made, that one or more of the scattered fibrotic areas may lie astride the path of the conducting tissue. Indeed, bundle branch block, first as a transient feature and later as a permanent fault, is

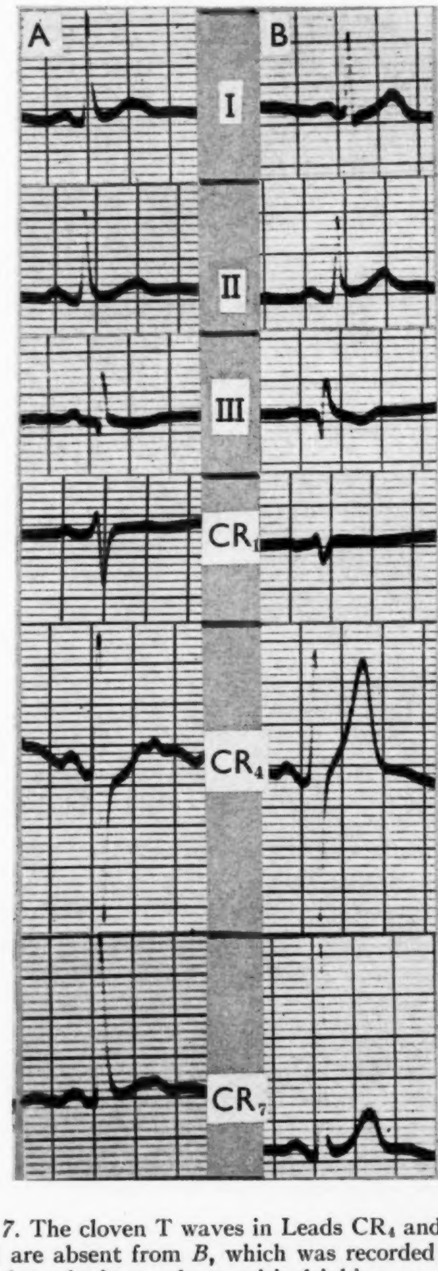

Fig. 7. The cloven T waves in Leads CR_4 and CR_7 in *A* are absent from *B*, which was recorded after complete abstinence from spirit-drinking.

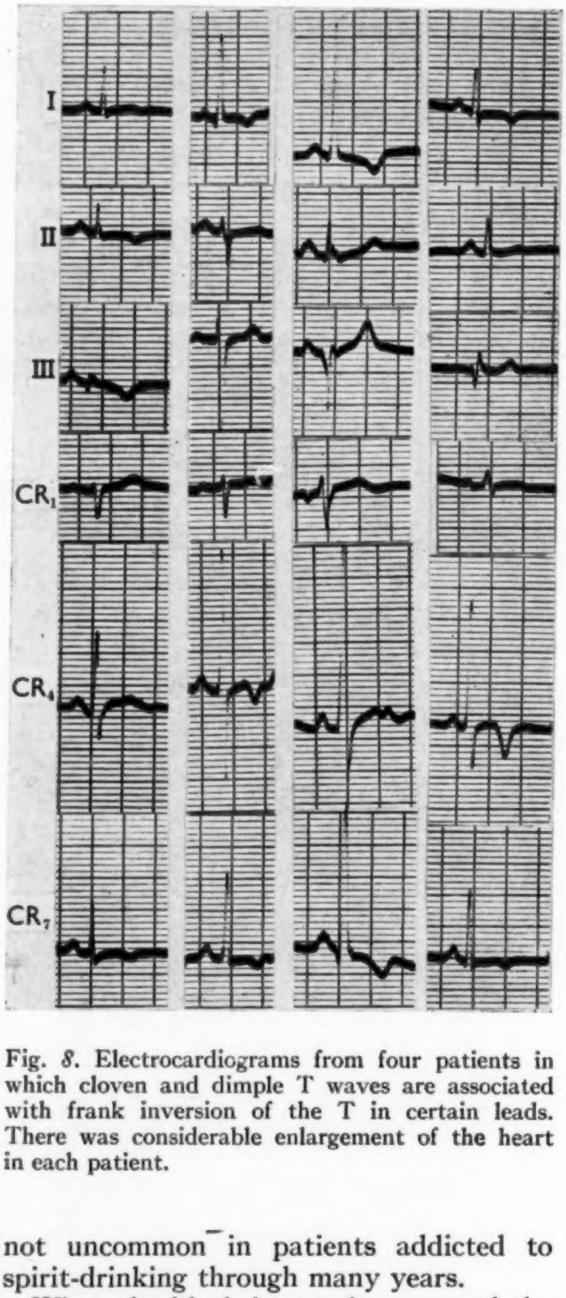

Fig. 8. Electrocardiograms from four patients in which cloven and dimple T waves are associated with frank inversion of the T in certain leads. There was considerable enlargement of the heart in each patient.

not uncommon in patients addicted to spirit-drinking through many years.

When the block is transient, one of the characteristic deformities of the T wave may be present in the standard electrocardiogram recorded when the block is absent (Fig. 11).

Examples of complete heart block, although less common than those exhibiting bundle branch block, are also not infrequently met with.

THE S_2S_3 PATTERN. Recently, we have shown that when the S wave in Leads II and III exceeds the R wave in the absence of an S in Lead I, a lesion is present in the anterolateral portion of the left ventricle. Naturally, the common cause of this fault is cardiac infarction from coronary arterial disease, but some other kind of cardiomyopathy may also supply the source. When it arises from alcoholic cardiomyopathy, a widening of the QRS complex may be an associated finding (Fig. 12).

The beriberi electrocardiogram. Mention has already been made of the fugitive T-wave inversion which takes place when alcoholism has produced a beriberi syndrome, and which appears immediately in the wake of thiamine therapy, reverting to normal in concert with the benefit which such therapy induces.

General remarks

Now that the clinical, pathologic, and electrocardiographic features of alcoholic cardiomyopathy have been described, some general questions remain to be considered which relate to the patient, and his work and habits.

What kind of man is he? He is usually a male and past middle age. As a rule, he meets his physician in private rather than in hospital practice. He is neither an outcast of society, a sloth in commerce, nor a sluggard in industry. On the other hand, he is sociable and likable, loyal to his colleagues and superiors, and a restless worker. Day in and day out he canvasses custom and hawks his ware as he fills and refills his guest's goblet and his own. On his return home he delves into the accumulated work of the day, fortifying himself far into the night from the bottle at his side. For a time the stimulant appears to stimulate his mind; in a longer time it poisons his heart, and he becomes a slave and the victim of the merciless competition inseparable from twentieth century commercialism.

Sometimes, he is the unhappy husband who, becoming estranged to his home, prefers to spend his evenings at the club or the bar, thereby avoiding the just admonishment of his wife, who sees more clearly than he does the approaching doom, in that through his stubborn disbelief that there is anything wrong, he is not impelled to modify his drinking habits.

Although he often plays at golf, he never excels at it, for he is more attracted to the amenities of the clubhouse than to improving his game. Another might be an aging

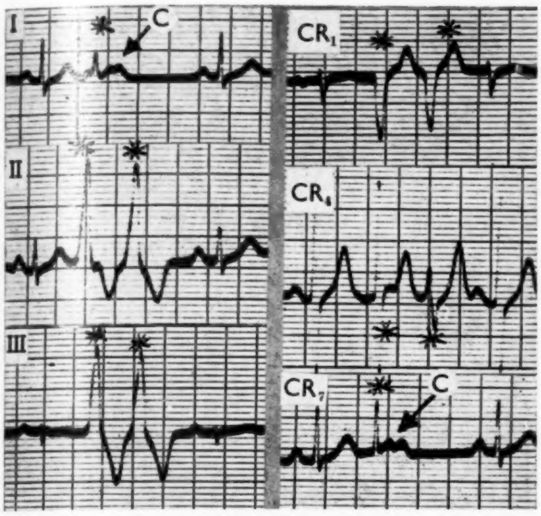

Fig. 9. Multiple extrasystoles (*) and moderate tachycardia. Cloven T wave (*C*) in two auricular extrasystoles.

bachelor without hobbies, who whiles away his hours of loneliness, and as he attempts to uplift his depressed spirits with alcohol, he drains his cup of sorrow in the false hope of removing his own.

Not infrequently, a patient's occupational association with the liquor trade as distiller or sampler, merchant or publican, brings to him an easy access to alcohol and to a habit which he tries in vain to resist or restrict.

How much does he drink? It is not difficult to ascertain the kind of alcohol consumed by patients presenting with alcoholic cardiomyopathy, and the order of preference proved to be whisky, gin, rum, brandy, and wine. Naturally, these were often taken in combination. If the consumption of alcohol was confined to beer, the syndrome described here was not met with, but of course beer was often taken in addition to spirits. When habitual excessive drinking is confined to beer, the beriberi syndrome is the likely manner in which the clinical picture presents itself.

An accurate estimate of the amount of alcohol consumed by individual patients, however, is seldom obtained. Nonetheless, persistent interrogation which uses finesse and artifice, when the meagerness of the admitted daily intake, for instance, is deliberately derided at first, may draw a confession to taking larger quantities and permit a truer view of the situation. Indeed, when the patient capitulates to this subtle questioning, he might resort to boastfulness and brag as one did, "I have taken two bottles of whisky each day for more than five years, and I have never once been drunk." It is constant drinking, not spasmodic inebriation, that poisons the heart. Another ruse which the interrogator, armed with trust in the electrocardiographic clue, can often use to extract from a patient a confession to drinking in excess of what he first names is to instruct the patient to abstain from drinking any alcohol because it is damaging the heart muscle, adding that since he only partakes of small quantities he would doubtless find it easy to conform with the request. This brings an admission that he does drink substantial quantities, and an appeal that a modified ration be allowed. At all times the ingenuity of the interrogator is pitted against the craftiness of the patient. In one such instance in which the interview had failed to draw an admission, as the patient turned to don his coat, a bulging hip-pocket came into view and subsequently was made the object of inquiry when a flask of brandy was uncovered, and was acknowledged to be a constant companion. Of course, the physician's reliable ally in his search for a true history is the spouse, unless, in rare in-

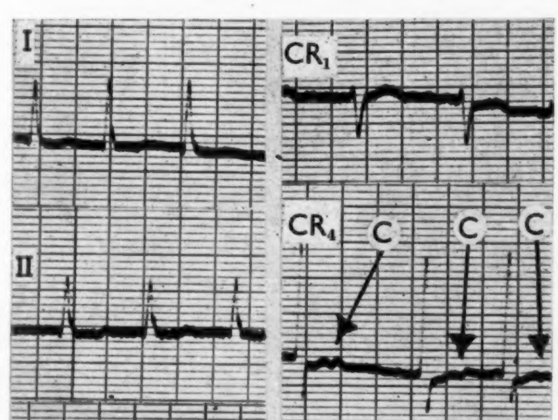

Fig. *10*. Cloven T waves (*C*) are apparent in Lead CR$_4$ in spite of the effects of digitalization in a patient with auricular fibrillation.

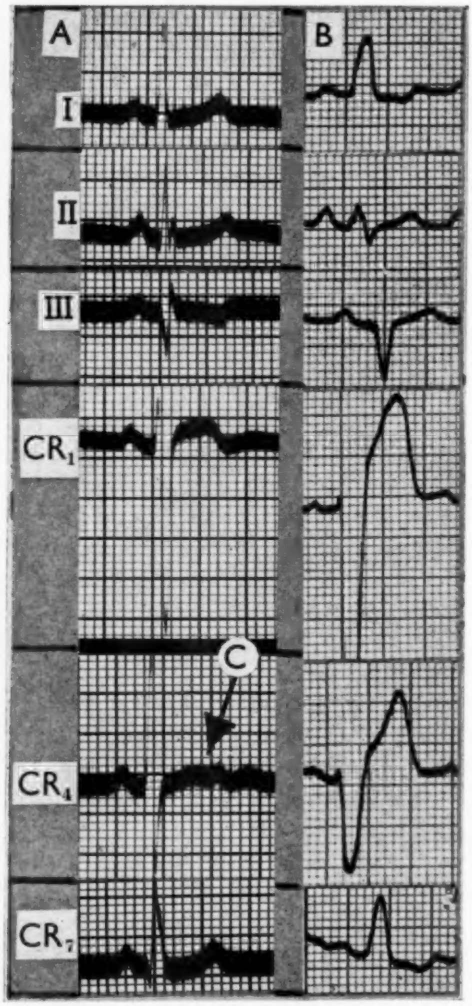

Fig. *11.* A cloven T wave (*C*) in Lead CR$_4$ in *A* is absent in *B* where left bundle branch block has supervened.

stances, the two are in collusion because of habits shared.

Although the electrocardiographic signs described here contribute to the recognition of alcoholic cardiomyopathy, they, too, cannot measure the quantity of alcohol which can produce the myocardial changes. Inseparable from the search for data that might provide information on the cardiotoxic dosage of alcohol is the appreciation that patients exhibit a different degree of tolerance to its deleterious effects, so that it is difficult to pronounce on what is enough and harmless, and what is excessive and harmful. To prejudge susceptibility in this context is not within the physician's competence. It is certain, however, that a daily consumption of 6 to 12 portions of spirits will produce cardiomyopathy in as many years, and in far less time in susceptible patients.

To most, the cost of the commodity is prohibitive, and for this reason alcoholic cardiomyopathy is less common among hospital than private patients, but the privilege of occupation whereby its cost might be debited to a business expense account, or its ready availability through the nature of one's work or trade, may make its actual cost a matter of less consequence. Those who crave spirits, and through financial sacrifice procure it, may share the sentiment of one patient, who, when asked how he afforded it, replied, "Doctor, you don't regard whisky at 37/6 (thirty-seven shillings and sixpence) a bottle as expensive when you have to pay 1/4 (one shilling and fourpence) for a cauliflower."

Treatment

This investigation does not permit one to moralize in regard to a national habit just because it is being abused, nor does it justify a plea to forego a conventional custom of entertaining a friend to casual drinks at a bar, at table, or in the home. It is concerned not with the consumption of alcohol as a sin to flee from, but with alcoholism as a dread disease to avoid. Its treatment is considered under three heads, namely, its prevention, and the management of the illness during its early and late phases.

Prevention. Prevention of alcoholic cardiomyopathy can only be effected through applied education, and wholesale dissemination of information about the injury to the heart which inevitably follows habitual spirit-drinking. This should become a national responsibility because it is of national concern. Because the habit is commonly formed in young adult life, arrangements for the matter to be clearly discussed in higher schools, colleges, and universities should become custom, and it must find a place in the official scholastic curriculum. Organized lectures need to be inaugurated among industrial and commercial societies, for it is in these groups that the habit so commonly finds first root. To be forewarned is to be forearmed, and prevention is better than cure, may both be hackneyed

phrases, but none can be more apt in a discussion of the treatment of alcoholic cardiomyopathy. Nor must medical opinion stand aloof to the problem of preventing this scourge of habitual excessive spirit-drinking, whose ravages on the heart have only recently come to light. Warning of its dangers must be tendered early. Such advice given and accepted will gain well-earned satisfaction. Advice given and thwarted will bring disappointment, though without guilt, to its counsellor. Advice withheld breeds guilt and remorse in that a duty has been neglected and an opportunity has passed.

The early phase. The early stage is identified when a patient presents with light symptoms, like moderate breathlessness or palpitation, and when characteristic signs in the electrocardiogram tell of the sparse changes in the myocardium, and the heart at cardioscopy shows only minimal or no cardiac enlargement. At this point the amber light has winked and the signal is at red, and failure to halt means a crash on the journey ahead. Advice to the patient must be sharp and peremptory, conveyed to him as a telling command in words implying total abstinence. At the start the patient often reacts indifferently to this strict injunction, for he regards nature as the villain that produces disease, and he is used to hire a doctor to cure it, so that he takes exception to a suggestion that the discomfort he suffers has been wrought at his own hand. When he is in this petulant mood, it takes time and patience to convince him of the seriousness of his illness. Even when he bends in understanding, he continues to plead for a reduced ration of the spirits which he has been told are poison to him, but the physician must stand firm, for nothing short of complete weaning will halt the march of the cardiac fibrosis.

Because the patient is usually overweight, his adherence to a reducing diet is to be urged, in the knowledge that he cannot lessen his grossness without foregoing alcohol.

The late phase. The late stage is recognized when breathlessness is a prominent symptom, and when the heart shows considerable enlargement with characteristic signs of heart failure. More severe changes have taken place in the myocardium, and the damage now is irretrievable. Because the characteristic signs in the electrocardiogram have been obscured by greater

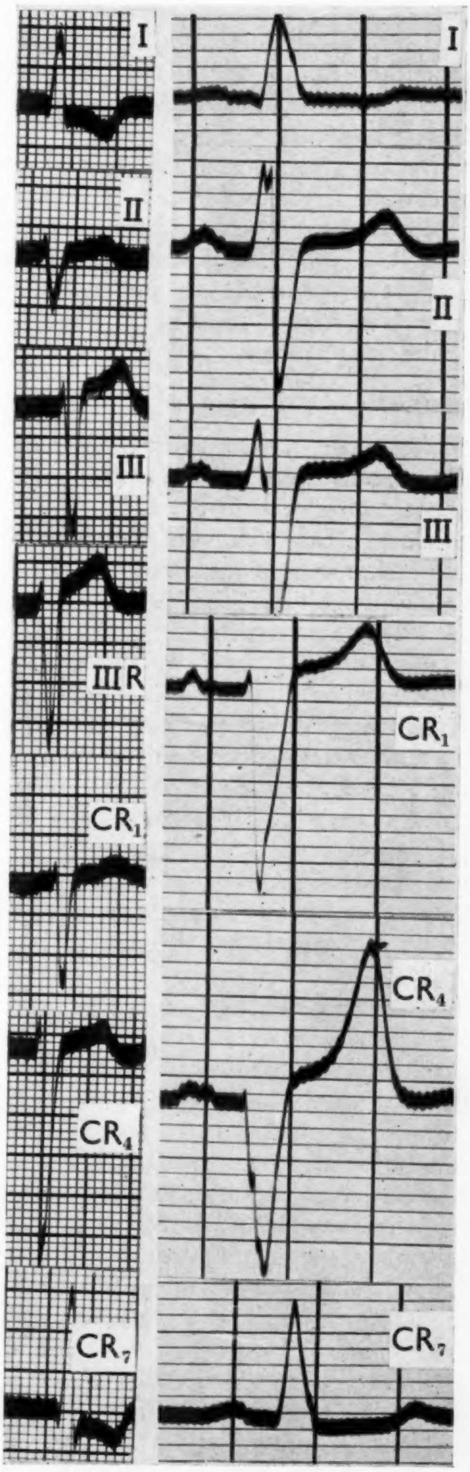

Fig. *12.* Deep S wave in Leads II and III; absent S in Lead I in 2 patients. QRS is a little wide.

deformities, heart failure from coronary arterial disease is often mistakenly diagnosed for alcoholic cardiomyopathy.

Treatment here has no high aspiration, and it is directed solely to the relief of the symptoms of heart failure. Thus, the intake of salt and fluid is restricted, and digitalis is prescribed along with oral diuretics. Thiamine should be added if a beriberi syndrome has supervened.

At its best, however, therapy at this stage can be little more than a palliative arrangement, for the opportunity to do real good has passed. This realization should spur effort to conclude an early diagnosis in order to introduce treatment before hope of recovery has faded.

Summary

Alcoholic cardiomyopathy is a common condition, and there are many reasons why our acceptance of this truth has been so long delayed. First, the stealth with which the condition sets in has made its recognition difficult. Next, the clinican has been accustomed to watch the deleterious effects of alcohol on the liver in the shape of fibrosis, and on the mind in the form of delirium tremens, and has been inattentive to its cardiotoxic effects unless these presented as the rare syndrome of beriberi. Again, the sparsity hitherto of signs which give proof that heavy spirit-drinking has caused heart failure, especially when a history of such overindulgence has been carefully concealed, has frustrated a true diagnosis. Moreover, whenever the electrocardiographic changes, here attributed to alcoholic cardiomyopathy, have been discovered in a patient with or without chest pain, they have too often been wrongly attributed to coronary arterial disease. Similarly, an abnormal rhythm like auricular fibrillation, when unassociated with one of its common causes, has been regarded too readily as arising from coronary disease.

The patient, more often male than female, is about middle age, and often a successful man of business. As a rule he is overweight, and this is often accepted as the cause of his moderate breathlessness, which is the most common presenting symptom. If palpitation should be the chief complaint, extrasystoles may be discovered alongside a moderate tachycardia, or the arrhythmia may take the form of paroxysmal or established auricular fibrillation. Other signs of cardio-arterial derangement are sparse or absent, although radiologically some slight enlargement of the heart may be detected.

During this early phase of the illness, when the changes in the myocardium are limited and scattered, the electrocardiogram can be a princely test, for it will show distinctive signs which compel a more persistent questioning of the patient in regard to his drinking habits. Such electrocardiographic signs include some form of arrhythmia, like extrasystoles, which are usually multiple and arise from diverse foci and occur in the presence of a moderate tachycardia, or auricular fibrillation. The T waves are deformed in a distinctive way, presenting a spinous, cloven, or dimple design, patterns which are not seen by themselves in the electrocardiogram of coronary arterial disease. Recognition of the illness at this stage is rewarding, because abstinence from spirit-drinking can halt the march of fibrosis in the myocardium and restore the patient to his customary health.

To miss the diagnosis, or to ignore advice on complete abstinence from spirit-drinking, leads inevitably to the more serious phase of the illness from more prolific myocardial fibrosis. In this event, breathlessness has progressed to become a menacing symptom, and the more obvious signs of heart failure make their appearance. These include a prominent venous pulse, systolic murmurs from mitral and tricuspid regurgitation, triple heart rhythm, considerable cardiac enlargement, pulmonary congestion, hepatic distention, and edema. The ECG changes are now more obvious, and the earlier distinctive T-wave patterns are submerged either by an arrhythmia, bundle branch block, complete heart block, or by a more frank inversion of the T. An S_2S_3 pattern is often added. Treatment in this circumstance can only be palliative in nature and directed to the alleviation of heart failure, for complete abstinence from spirit-drinking cannot alter the substantial myocardial changes. Thus, digitalization, oral diuretics, restricted intake of fluid and sodium, and thiamine, if the syndrome of beriberi has been added, are the orthodox remedies to be given, but without hope of producing lasting improvement.

The salutary lessons collected from a study of alcoholic cardiomyopathy are that the condition is common, and that it commonly goes unrecognized until it reaches a stage at which the myocardial fibrosis can neither be halted nor improved by any form of treatment. In the early phase of the illness, abstinence from spirit-drinking can arrest the myocardial injury. Clearly, therefore, the need is for early recognition of the condition, when attention to its distinctive electrocardiogram will make this possible.

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Annotations

On the neglected role of water and potassium in cardiovascular therapy

The use of low-sodium diets, diuretics, and digitalis occupies a time-honored and rather well-defined role in the therapy of cardiac patients. However, in spite of the vigorous and correct use of such methods the general practitioner, as well as the consulting cardiologists, is all too often faced with patients who are seemingly refractory to all types of currently accepted medical and surgical therapy.

The matter of how much water to allow the cardiac patient is much less clear, and the marked restriction of water has been questioned by several workers.[1,2] The majority of physicians probably permit patients with cardiac problems to take liquids ad libitum. The intake of water is then dependent on the sensation of thirst, which varies from patient to patient, is influenced by habit and environmental circumstances, and may even be depressed because of cardiac failure. This permissive approach usually means that the volume of liquids imbibed is much less than the minimum requirement for the optimal elimination of the retained sodium and water. There have been studies which demonstrated that the volume of liquid imbibed during a low-sodium regimen is a most important factor in the results obtained.[3-6]

In regard to potassium a considerable literature has accumulated, indicating that in cardiac failure there is usually an intracellular deficit of potassium even though the levels of serum potassium seem to be normal. Selye[7] has suggested experimentally that potassium exerts a "protective role" on the myocardium. Furthermore, successful diuresis causes added loss of potassium, particularly if the newer saluretic drugs are used. Thus, it is quite possible that potassium, too, may be an important part of the therapy of every cardiac patient, with due regard to the renal involvement present.

Recently, a report was made of the experience of several years with a large group of patients in whom careful attention was paid to the intake of water and the supplementary use of potassium.[8] The regimen evolved is quite similar to that generally accepted for cardiac patients in terms of restriction of sodium and adequate intake of protein. The essential difference is in the fact that water was actually prescribed in each case in amounts which usually averaged between 2,500 and 3,000 c.c. daily as natural water. This high intake of water is similar in amount to that used in the studies previously alluded to and, in our experience, much higher than the intake in the patient who is allowed water ad libitum.

Potassium chloride, 1.5 to 3 Gm., was also given daily in divided doses. Levels of serum potassium were maintained above 4.2 mEq. per liter, since at levels below this value, electrocardiographic signs of low potassium, extrasystoles, and paroxysmal tachycardias were often encountered. We believe, therefore, that the commonly used lower limit of normal of serum potassium, i.e., 3.7 mEq. per liter, may represent hypopotassemia for cardiac patients.

This approach was used with surprising and gratifying clinical success in practically all types of cardiac involvement, i.e., cardiac failure (particularly the refractory type), hypertension, angina pectoris, and chronic cor pulmonale. In many instances it was possible to decrease and even discontinue the use of diuretics, digitalis, and the various hypotensive agents. Most important of all the patient's weight and sense of improvement were the major parameters of successful use of the regimen. Naturally, some practice on the part of the physician is necessary to titrate each individual case, as is an acquaintance with some of the reasons for seeming failure as detailed in the report.[8]

Resano[9] has independently studied a group of 26 cardiac patients in great detail, using the principles of this regimen. His findings are extremely interesting, not only because he was able to achieve success but because of his observations. If the intake of water was kept at levels of 1,500 to 2,000 c.c., then intake and output were approximately equal. However, when he increased the intake of water of his patients to 2,500 c.c., he achieved a diuresis of at least 3,000 c.c., or, in other words, output exceeded intake by 500 c.c. Finally, at these levels of higher intake he did not observe the so-called "dilution syndrome."

These findings make it appear likely that water and potassium are of more value in the therapeutic armamentarium for cardiovascular disease than is commonly realized. It is suggested that the observations on the ad libitum use of water, as well as the benefits to be derived from a higher intake of water by patients with cardiovascular disease, can be easily checked by almost any physician who sees general medical cases. Finally, more studies are needed in order to clearly delineate the usefulness and mechanisms of the low-sodium, high-water, high-potassium regimen.

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Significance of reticuloendothelial cells in atherosclerosis

The relationship between lipid metabolism and atherosclerosis has led to investigations into the part played by cells of the reticuloendothelial system in both these processes. It has been thought for many years that reticuloendothelial cells may be involved in lipid metabolism,[1,2] and the presence of macrophages in plaques in the walls of blood vessels suggests that these cells may also be important in the pathology of atherosclerosis. Recent work indicates that Kupffer cells of the liver and the tissue macrophages may influence the development of experimental atherosclerosis in two distinct ways.

It appears that the Kupffer cells may have some special role in removing cholesterol from the blood stream. After the feeding of cholesterol to, or the intravenous injection of turbid hypercholesterolemic serum into, rats, the Kupffer cells were found to be filled with cholesterol.[3] These cells have also been shown to have a significantly higher content of cholesterol and cholesterol ester than do the hepatic parenchymal cells.[4] The breakdown and subsequent excretion of cholesterol also appears to be related to the activity of the Kupffer cells. In rats fed on a high-fat, high-cholesterol diet, it has been found that if the activity of the reticuloendothelial system is stimulated by intravenous injections of zymosan, the levels of cholesterol, cholesterol ester, and triglycerides in the plasma and liver are significantly lower than in control animals.[5] These findings suggest that the concentration of cholesterol in the plasma and other tissues may be related to the activity of the Kupffer cells.

In regard to the atherosclerotic lesion itself, macrophage cells filled with lipid have been shown to attach themselves specifically to areas of the aorta overlying atheromatous plaques.[6] These cells have been seen passing through the aortic endothelium in cholesterol-fed rabbits. It is not known whether these macrophages are in the process of leaving the blood stream or whether they are being mobilized from within the arterial wall.

It may be that macrophages play some part in preventing the accumulation of lipids in the tissues. Macrophages could do this in two ways. They could ingest the material and transport it to some other site, such as the lungs or the gut, where it may be excreted, or they could take up the lipid and metabolize it themselves. The movement of lipid-filled macrophages into or out of the arterial wall has been mentioned. In ear chambers, which were established in cholesterol-fed rabbits, macrophages have been seen lying alongside the growing tips of blood capillaries, and these cells exhibit the characteristic birefringence associated with the spherocrystals of cholesterol when cholesterol is seen under polarized light.[7] Reticular cells in lymph nodes also take up and store cholesterol and cholesterol esters readily.[8]

Once in the macrophage, the lipids are exposed to the enzyme systems of the cell. Histologically, macrophages that have taken up cholesterol show an increased sudanophilia after a few days. This change is associated with the accumulation of fatty acids within the cells. Cholesterol can be esterified and cholesterol esters can be hydrolyzed by macrophages,[9] and these cells are also capable of hydrolyzing and oxidizing triglycerides and fatty acids to carbon dioxide and water.[10] The exact significance of these transformations is not yet known, but they may be related in some way to the role of these cells in removing lipids which accumulate in relatively avascular areas of the body.

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Pulmonary second sound in the tetralogy of Fallot

The second heart sound in the pulmonary area in patients with cyanotic tetralogy of Fallot is single and produced by closure of the aortic valve (A_2), the pulmonary element being inaudible and only rarely recorded in the phonocardiogram.[1-5] It has been suggested that the absence of the pulmonary component (P_2) in Fallot's tetralogy is due to low levels of pulmonary flow, most of the right ventricular output being shunted to the systemic circulation.[2] This was supported by the appearance of P_2 after pulmonary valvotomy or subclavian-pulmonary anastomosis,[2] when the pulmonary flow increases, and by not uncommonly recording P_2 in the so-called acyanotic tetralogy, in which the pulmonary flow is not diminished. Comparison of the magnitude of pulmonary flow of patients with pulmonary stenosis and that of patients with Fallot's tetralogy shows that it may be quite low in cases of severe pulmonary stenosis and comparable to the levels observed in the average case of cyanotic tetralogy.[2] In severe pulmonary stenosis, however, P_2 is not uncommonly recorded.[6] Investigation of the effect of norepinephrine in pulmonary stenosis and in the tetralogy showed that accentuation of P_2 or its appearance on the phonocardiogram, if it was not recorded prior to the administration of the amine, will frequently occur in severe pulmonary stenosis, but not in the tetralogy.[7] It seems likely, therefore, that other factors in addition to pressure (and flow) are responsible for the absence of P_2 in the tetralogy. Such factors may be: (a) deformity of the pulmonary valve and hypoplastic main pulmonary artery, resulting in inadequate cusp excursion toward the closed position; (b) dorsal displacement of the pulmonary valve and artery accompanying the aortic override.[6] In view of the poor conduction of sound through the lung tissue[8] this results in attenuation of P_2, whereas the frontal position of the aorta is held responsible for the loud A_2. Maximal dorsal displacement of the pulmonary valve is encountered in transposition of the great vessels: absence of P_2 with loud A_2 have, in fact, been described in transposition with pulmonary stenosis.[9,10] Absence of P_2 is also noted in transposition with increased pulmonary flow and normal pulmonary arterial pressure.[11] Conversely, absence of aortic override is probably, at least in part, responsible for the audible P_2 in several cases of acyanotic tetralogy. As a final point, it may be mentioned that, when distance is not involved, as in intracardiac phonocardiograms, P_2 is invariably recorded in patients with the tetralogy.[12]

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Medicine versus science

The goal of science is the discovery of truth, whereas the goal of medicine is the prevention and cure of disease in man. Usually, these two goals can be harmonized and science can be harnessed to serve medicine, but there are conflicts, and the issues in such conflicts should be made as clear as possible.

It is often said, for example, that the burden of proof rests with the physician who states that a drug or form of treatment is beneficial in a certain disease, and, in a scientific sense, this is justified. Is the implication, however, that all physicians should withhold such treatment until proof of its efficacy is incontrovertible, equally justified? Such a position is in accord with the traditions of science, but it may sometimes be challenged from the point of view of medicine.

Suppose, for example, that a new drug is available for the treatment of a chronic disease. Suppose also that it has been demonstrated that its short-term, and even long-term, side actions are negligible, and that it is not demonstrably toxic. Suppose also that the disease it is purported to control is not only productive of morbidity but potentially lethal, and that because of its chronicity an incontrovertible answer with reference to efficacy of drug therapy will not be available for 15 to 20 years. Where is the moral burden here from the point of view of medicine and its goals? Is it justified to withhold such treatment in the name of science?

It seems to me that when there is a reasonable chance that a form of treatment may be effective, and if there are not demonstrable adverse effects, the patient should be given the benefit of doubt. The saving of life is more important than proving a point. On the other hand, if the doubt as to efficacy is strong enough and the evidence as to lack of toxicity is weak enough, such treatment should be withheld. This is one of the areas in which the erudition and judgment of the individual physician has its greatest exercise. There is a region of doubt in this area, moreover, where the scientific evaluation of the efficacy of treatment in a controlled experiment involving the planned exhibition as well as the withholding of the drug is needed and justifiable. It cannot be overemphasized, however, that for the individual physician the decision to prescribe or not to prescribe may be a moral one pending rigid scientific proof or disproof of the efficacy of a drug. If the goal of science has been attained and such evidence is available, there is no conflict. In the interim, however, the goal of medicine must still be pursued.

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The kinked left innominate vein

A certain charm lies in original observations about simple phenomena, especially when these must have been seen repeatedly but passed unnoticed by others. In 1935, L. G. Sabathié[1] drew attention to engorgement of the left external jugular vein as "un nuevo signo periférico en las aortopatías." However, the sign, and Sabathié's observation of it, appear to have largely escaped the notice of English-speaking cardiologists until 1960, when K. S. Smith[2] described the significance of the "kinked left innominate vein," and G. Lista[3] drew attention to the priority of Sabathié.

Both Sabathié and Smith published convincing photographs of unilateral, or predominantly unilateral, engorgement of the left external jugular vein. Theoretically, the anatomic disposition of the left innominate vein makes it easy to understand how the vein might be compressed should the aortic arch rise higher than its usual position. Pertinent here is the relatively low pressure of blood in the thin-walled innominate vein and the anterior location of the vessel close to the bony thorax, where it may readily be compressed by any expanding structure, including an aortic arch. High arterial pressure may displace the aortic arch upward and unfold it, whereas arteriosclerosis may allow elongation even in the absence of hypertension. Similar changes in the arterial trunks that spring from the arch behind the left innominate vein may contribute to the compression. A rigid aortic arch, often found with atheroma and calcification, is more likely to interfere with neighboring venous flow than is an aorta dilated dynamically and exerting only intermittent pressure.

All five of Smith's published cases had arterial hypertension, and radiographs indicated an abnormally high aortic arch, plus either unfolding or obvious atheroma. There was no evidence of other cause of left innominate vein obstruction. Venous pressure measurements showed elevation in the venous system of the left arm as well as the left side of the neck, indicating obstruction proximal to the junction of subclavian and innominate veins. Sabathié had also recorded similar radiographic findings in such cases and noted that the venous pressure in the left antecubital vein was higher than that in the right.

Smith pointed out that the unilateral engorgement of the left external jugular vein, as a sign of a kinked left innominate vein, is in some ways a counterpart of the kinked right common carotid artery described by Parkinson and Bedford,[4] both signs being attributed to a high and probably rigid aortic arch. Clinically, a systolic thrust or pulsation visible or palpable at the upper chest or suprasternal notch may permit diagnosis of an enlarged or elongated aortic arch. Otherwise, there are few dependable signs. The kinked right carotid artery is a valuable sign but is almost entirely confined to women. The unilateral engorgement of the left external jugular vein is an additional important piece of evidence and is found as often in men as in women. Both Sabathié and Smith admitted that other causes of obstruction of the left innominate vein could also produce the sign, for example, neoplasm.

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Book reviews

VISUAL AIDS IN CARDIOLOGIC DIAGNOSIS AND TREATMENT. Edited by Arthur M. Master, Consultant in Cardiology, The Mt. Sinai Hospital, New York; Chairman, Cardiovascular Disease Section, Committee on Scientific Program, American College of Chest Physicians, June, 1959; and Ephraim Donoso, M.D., Research Assistant in Cardiology, The Mt. Sinai Hospital, New York. New York, 1960, Grune & Stratton, Inc., 216 pages. Price $10.

Merlin had the difficult task of building up the magical powers of the sword Excalibur without detracting from its wielder King Arthur. His aim was to make the King appear fortunately blessed in possessing such a weapon but also neither unskillful nor naive in trusting the magic blade. The editors and authors of this volume were faced with an analogous difficulty in crediting instrumental advance without discrediting clinical acumen.

There are several well-written, well-illustrated chapters which can serve as concise reference summaries for the general medical reader—specifically, those chapters on shunt localization by indicator-dilution techniques, angiocardiography, and selective angiocardiography. As may be expected in a collection originating from a symposium, there are also "filler" chapters of only transient worth. Chapters of intermediate quality are concerned largely with defining or exercising the special vocabularies in the different areas of cardiographic or cardiologic interest. (In this connection, the published recommendations of the New York Heart Association as to nomenclature did *not* influence the choice of terms in the phonocardiographic discussion of valvular regurgitation.) One item which will provoke the curiosity or skepticism of physicians is the mere mention of a pathognomonic third sound detected in the right ventricular phonocardiogram in constrictive pericarditis; no discussion or explanation of the distinctive nature of the finding is given.

So many of the authors saluted the organized team that this reader has come to hope that further aids and advances in cardiologic diagnosis and treatment will permit a return of emphasis toward heightened individual competence and away from a feudal division of cerebration and responsibility.

CARDIOVASCULAR DISEASES. By David Scherf, M.D., F.A.C.P., Professor of Clinical Medicine, New York Medical College, Flower and Fifth Avenue Hospitals; and Linn J. Boyd, M.D., F.A.C.P., Professor and Director of Medicine, Flower and Fifth Avenue Hospitals, New York. Third edition, New York, 1958, Grune & Stratton, Inc., 829 pages. Price $18.50.

It has been nearly ten years since the second edition of this textbook appeared, and during that time great strides in medical progress have been made. Not the least of these advances has been in cardiology, such as electrocardiography, cardiac catheterization, angiocardiography, and the diagnostic enzymes. The book is written with emphasis on historical data, physical diagnosis, and clinical judgment, and this is certainly worth while, but it is unfortunate that more detail was not devoted to these more recent diagnostic procedures.

The paucity of electrocardiographic illustrations is a shortcoming, and the reader is told that he must purchase the authors' text on that subject for more comprehensive information. Some of the electrocardiograms shown are not labeled, and as such may be confusing. Much of the information is derived from the wide and varied experience of the authors and is written from such a standpoint in a style that is enjoyable and easily read. There is an extensive bibliography with complete titles, and many classic articles are included.

In a work covering the broad field of cardiovascular disease there are bound to be ideas that will not meet general agreement. The authors' awareness of this is indicated in the statement, "When the use of leeches is recommended, one often encounters a smile of pity." The use of leeches is suggested for acute engorgement of the liver in congestive heart failure and thrombophlebitis. In light of more recent therapeutic agents this hardly seems necessary. Despite these objections and a few others the book covers the field of cardiovascular disease in an informative and entertaining manner. Students and interns will find the book useful, but it is not recommended for specialists in the field.

Announcements

The University of Colorado School of Medicine announces the Cochems Competition, funds for which were provided in the will of the late Mrs. Jane Nugent Cochems. A prize of $2,500 will be awarded to the author of the best paper on the subject of "The Diagnosis, Etiology and Treatment of Thrombophlebitis." The competition is open to all physicians, and entries must be received, in triplicate, on or before Oct. 1, 1961.

The Colorado National Bank of Denver, Trustee under the will of Jane Nugent Cochems, has requested the Dean of the University of Colorado School of Medicine to conduct the competition. The judges, appointed by him, are Dr. Michael E. DeBakey, Professor and Head of the Department of Surgery, Baylor University College of Medicine, and Dr. Sol Sherry, Professor of Medicine, Washington University School of Medicine.

Papers submitted in the competition may not be published until after the winner of the competition has been announced. At that time, the winning paper and all others may be published at the discretion of individual authors. It should be noted, however, that those involved in conducting the competition will not assume any responsibility for submitting manuscripts for publication nor for any costs incident thereto. The winning paper, if published, must carry the designation, "Awarded the Jane Nugent Cochems Prize."

Questions regarding the competition and all manuscripts should be directed to Dr. Robert J. Glaser, Vice-President for Medical Affairs and Dean of the University of Colorado School of Medicine, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 20, Colo.

A seminar on Pediatric Cardiology, sponsored by the medical staff, will be held at Childrens Memorial Hospital, Omaha, Nebraska, on May 8, 1961. Principal speakers will be C. Walton Lillehei, M.D., Professor of Surgery, University of Minnesota, and James W. DuShane, M.D., Section of Pediatrics, Mayo Foundation, Associate Professor of Pediatrics, University of Minnesota.

A complete program and registration blank may be obtained by writing to Postgraduate Seminar, Childrens Memorial Hospital, Omaha 5, Nebraska.

Courses for Physicians in Nonsurgical Method of Reviving Stopped Hearts. The American Heart Association has announced that it has scheduled 20 half-day courses in nine cities throughout the nation in which physicians will be instructed in a new, nonsurgical method of restoring the beat to a stopped heart. The first of these teaching sessions was held on January 25, in New York City, for invited physicians from the upper Atlantic region.

Known as "closed chest cardiac resuscitation," the new technique has received wide attention in the medical profession since it was first described some months ago by a team of scientists at Johns Hopkins Hospital (Baltimore). The Johns Hopkins team, which includes Dr. W. B. Kouwenhoven, Dr. James R. Jude, and Dr. G. Guy Knickerbocker, has agreed to serve as instructors for the courses sponsored by the Heart Association. In addition, the February issue of the Heart Association's monthly publication for physicians, *Modern Concepts of Cardiovascular Disease*, was devoted to an article on this subject by the Johns Hopkins group.

Previous methods of starting up a stopped heart required either administration of an electric shock or opening of the chest in order to massage the heart by hand. In the closed chest technique, reliance is placed primarily on controlled, intermittent pressure of the hands placed over the patient's breastbone.

When correctly applied, this method has been found to be successful in restoring the heartbeat in 70 per cent of cases. Its application by untrained persons is not without hazard, however, and for this reason the professional teaching institutes have been arranged. Physicians invited to attend the first 20 courses will be expected to conduct similar teaching sessions for other doctors in their home communities, the Heart Association said, with a view to disseminating information on the new technique throughout the United States. It is not planned at the present time to teach the method to nonprofessional persons.

Physicians who wish to attend one of these teaching sessions are asked to communicate with their local Heart Association affiliate. In each case, separate morning and afternoon courses of 3 hours will be held, with attendance at each limited to 50 physicians. In addition to the opening sessions in New York, courses were scheduled for February 1 in Los Angeles, and subsequently in other cities to be announced.

The Annual Convention of the National Geriatrics Society, will be held on May 1-4, 1961, at the St. Francis Hotel, San Francisco, Calif.

For further information write to Ira O. Wallace, President, National Geriatrics Society, 5 Park Towne South, Philadelphia 30, Pa.